```
=> d que stat l44
L7              QUE  ABB=ON  PLU=ON  AY<2004 OR PY<2004 OR PRY<2004 OR MY
                <2004 OR REVIEW/DT
L8              QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9              QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10             QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                 OR (4(W)MER)
L12             QUE  ABB=ON  PLU=ON  HEAT OR HEATING OR HEATED OR HEATS O
                R PREHEAT? OR (PRE(W)HEAT?) OR TEMP OR TEMPERATURE
L13             QUE  ABB=ON  PLU=ON  AGE OR AGING OR AGEING OR AGES OR AG
                ED OR TIME
L14             QUE  ABB=ON  PLU=ON  HEMOGLOBINS+PFT,OLD,NT/CT
L15             QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L19         869 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 (L) L9
L20         143 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 (L) L10
L21         630 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 (L) L15
L22          42 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L19 OR L20) AND L21
L23          12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 AND L20
L24          52 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L22 OR L23)
L25        2269 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (10A) L9
L26        1145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (10A) L10
L27        2209 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (10A) L15
L28         164 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND L27
L29         131 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L27
L30          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND L29
L31          70 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 OR L30
L32          20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND (L12 OR L13)
L33          65 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32) AND L7
L35          21 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND (?TETRAMER?/OBI OR
                (TETRA/OBI(W)MER?/OBI) OR 4MER/OBI OR (4/OBI(W)MER/OBI))
L36          38 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND (?POLYMER?/OBI OR
                POLYMD/OBI OR ?OLIGOMER?/OBI)
L37          39 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND (STABILI?/OBI OR
                STABL?/OBI)
L38          54 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L35 OR L36 OR L37)
L39          64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L14
L40          53 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L38 AND L39
L41          21 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L40 AND (L12 OR THERM? OR
                L13)
L42          43 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L21
L43          15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 AND L42
L44          43 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L42 OR L43)


=> d que stat l60
L48         281 SEA FILE=WPIX ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX
                OR HB/BIX) (10A) (STABILI?/BIX OR STABL?/BIX)
L49         295 SEA FILE=WPIX ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX
                OR HB/BIX) (10A) (?POLYMER?/BIX OR POLYMD/BIX OR ?OLIGOMER?/BIX
                )
L50          46 SEA FILE=WPIX ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX
                OR HB/BIX) (10A) (?TETRAMER?/BIX OR (TETRA/BIX(W)MER?/BIX) OR
                4MER/BIX OR (4/BIX(W)MER/BIX))
L51          11 SEA FILE=WPIX ABB=ON  PLU=ON  L48 AND L50
L52          32 SEA FILE=WPIX ABB=ON  PLU=ON  L48 AND L49
L53          20 SEA FILE=WPIX ABB=ON  PLU=ON  L49 AND L50
L54          51 SEA FILE=WPIX ABB=ON  PLU=ON  (L51 OR L52 OR L53)
L55          51 SEA FILE=WPIX ABB=ON  PLU=ON  L54 AND (AY<2004 OR PY<2004 OR
                PRY<2004)
L56          37 SEA FILE=WPIX ABB=ON  PLU=ON  L55 AND L48
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L57          25 SEA FILE=WPIX ABB=ON  PLU=ON  L55 AND L50
L58          11 SEA FILE=WPIX ABB=ON  PLU=ON  L56 AND L57
L59           7 SEA FILE=WPIX ABB=ON  PLU=ON  L58 AND ((HEAT/BIX OR HEATING/BIX
                 OR HEATED/BIX OR HEATS/BIX OR PREHEAT?/BIX OR (PRE/BIX(W)HEAT?
                 /BIX) OR TEMP/BIX OR TEMPERATURE/BIX) OR (AGE/BIX OR AGING/BIX
                 OR AGEING/BIX OR AGES/BIX OR AGED/BIX OR TIME/BIX) OR THERM?/BI
                 X)
L60          11 SEA FILE=WPIX ABB=ON  PLU=ON  L58 OR L59


=> d que stat l84
L7               QUE  ABB=ON  PLU=ON  AY<2004 OR PY<2004 OR PRY<2004 OR MY
                 <2004 OR REVIEW/DT
L8               QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9               QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10              QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                  OR (4(W)MER)
L12              QUE  ABB=ON  PLU=ON  HEAT OR HEATING OR HEATED OR HEATS O
                 R PREHEAT? OR (PRE(W)HEAT?) OR TEMP OR TEMPERATURE
L13              QUE  ABB=ON  PLU=ON  AGE OR AGING OR AGEING OR AGES OR AG
                 ED OR TIME
L15              QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L68              QUE  ABB=ON  PLU=ON  HEMOGLOBINS+PFT,OLD,NT/CT
L69        1358 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8(15A)L15
L70         692 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8 (10A) L10
L71        1173 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8 (10A) L9
L72        2250 SEA FILE=MEDLINE ABB=ON  PLU=ON  L68 AND (L69 OR L70 OR L71)
L73         923 SEA FILE=MEDLINE ABB=ON  PLU=ON  L72 AND L69
L74         148 SEA FILE=MEDLINE ABB=ON  PLU=ON  L73 AND (L70 OR L71)
L75         107 SEA FILE=MEDLINE ABB=ON  PLU=ON  L74 AND L10
L76         101 SEA FILE=MEDLINE ABB=ON  PLU=ON  L75 AND L7
L77        1320 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8 (15A) (L12 OR THERM?)
L78        6399 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8 (15A)L13
L79          25 SEA FILE=MEDLINE ABB=ON  PLU=ON  L76 AND (L77 OR L78)
L82          12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L79 AND L9 AND L10
L83          25 SEA FILE=MEDLINE ABB=ON  PLU=ON  L79 AND L15
L84          12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L82 AND L83


=> d que stat l108
L7               QUE  ABB=ON  PLU=ON  AY<2004 OR PY<2004 OR PRY<2004 OR MY
                 <2004 OR REVIEW/DT
L8               QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9               QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10              QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                  OR (4(W)MER)
L11              QUE  ABB=ON  PLU=ON  ?PYRIDOX?
L12              QUE  ABB=ON  PLU=ON  HEAT OR HEATING OR HEATED OR HEATS O
                 R PREHEAT? OR (PRE(W)HEAT?) OR TEMP OR TEMPERATURE
L13              QUE  ABB=ON  PLU=ON  AGE OR AGING OR AGEING OR AGES OR AG
                 ED OR TIME
L15              QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L90              QUE  ABB=ON  PLU=ON  HEMOGLOBIN+PFT,OLD,NT/CT
L91              QUE  ABB=ON  PLU=ON  "POLYMERIZED HEMOGLOBIN"+PFT,OLD,NT/
                 CT
L92              QUE  ABB=ON  PLU=ON  "HEMOGLOBIN DERIVATIVES"+PFT,OLD,NT/
                 CT
L93        1327 SEA FILE=EMBASE ABB=ON  PLU=ON  L8(15A)L15
L94         713 SEA FILE=EMBASE ABB=ON  PLU=ON  L8(15A)L10
L95        1311 SEA FILE=EMBASE ABB=ON  PLU=ON  L8(15A)L9
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L96          20 SEA FILE=EMBASE ABB=ON  PLU=ON  L93 AND L94 AND L95
L98             QUE  ABB=ON  PLU=ON  "HEMOGLOBIN DERIVATIVE"+PFT,OLD,NT/C
                T
L99        2318 SEA FILE=EMBASE ABB=ON  PLU=ON  ((L90 OR L91 OR L92) OR L98)
                AND (L93 OR L94 OR L95)
L100        933 SEA FILE=EMBASE ABB=ON  PLU=ON  L99 AND L93
L101        105 SEA FILE=EMBASE ABB=ON  PLU=ON  L100 AND L94
L102         20 SEA FILE=EMBASE ABB=ON  PLU=ON  L101 AND L95
L103         20 SEA FILE=EMBASE ABB=ON  PLU=ON  L96 OR L102
L104         14 SEA FILE=EMBASE ABB=ON  PLU=ON  L103 AND (L11 OR L12 OR L13 OR
                THERM? OR PRESERV? OR STORE OR STORAGE OR STORING OR STORED)
L105         20 SEA FILE=EMBASE ABB=ON  PLU=ON  L103 OR L104
L106         16 SEA FILE=EMBASE ABB=ON  PLU=ON  L105 AND L7
L107         16 SEA FILE=EMBASE ABB=ON  PLU=ON  L106 AND L15
L108         16 SEA FILE=EMBASE ABB=ON  PLU=ON  L106 OR L107


=> d his l121

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, BIOENG, LIFESCI, CABA, BIOTECHNO,
     BIOTECHDS, VETU, VETB, DRUGU, DRUGB, SCISEARCH, CONF, CONFSCI, DISSABS'
     ENTERED AT 10:12:38 ON 12 MAY 2006)
L121         51 S L119 OR L120
                SAVE TEMP L121 MOH516MUL1B/A

     FILE 'STNGUIDE' ENTERED AT 10:29:38 ON 12 MAY 2006

=> d que stat l121
L7              QUE  ABB=ON  PLU=ON  AY<2004 OR PY<2004 OR PRY<2004 OR MY
                <2004 OR REVIEW/DT
L8              QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9              QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10             QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                 OR (4(W)MER)
L11             QUE  ABB=ON  PLU=ON  ?PYRIDOX?
L12             QUE  ABB=ON  PLU=ON  HEAT OR HEATING OR HEATED OR HEATS O
                R PREHEAT? OR (PRE(W)HEAT?) OR TEMP OR TEMPERATURE
L13             QUE  ABB=ON  PLU=ON  AGE OR AGING OR AGEING OR AGES OR AG
                ED OR TIME
L15             QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L114       2198 SEA L8(10A) L10
L115       5045 SEA L8(15A) L15
L116        349 SEA L114 AND L115
L117       4628 SEA L8 (10A) L9
L118         61 SEA L116 AND L117
L119         51 SEA L118 AND L7
L120         38 SEA L119 AND (L11 OR L12 OR L13 OR THERM? OR PRESERV? OR STORE
                OR STORAGE OR STORING OR STORED)
L121         51 SEA L119 OR L120


=> dup rem l44 l60 l84 l108 l121
DUPLICATE IS NOT AVAILABLE IN 'CONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 10:31:15 ON 12 MAY 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIX' ENTERED AT 10:31:15 ON 12 MAY 2006
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FILE 'MEDLINE' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'EMBASE' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'BIOSIS' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'PASCAL' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'BIOENG' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'LIFESCI' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'BIOTECHNO' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'DRUGU' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'SCISEARCH' ENTERED AT 10:31:15 ON 12 MAY 2006

FILE 'DISSABS' ENTERED AT 10:31:15 ON 12 MAY 2006

PROCESSING COMPLETED FOR L44
PROCESSING COMPLETED FOR L60
PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L108
PROCESSING COMPLETED FOR L121
L122 77 DUP REM L44 L60 L84 L108 L121 (56 DUPLICATES REMOVED)
ANSWERS '1-43' FROM FILE HCAPLUS
ANSWERS '44-51' FROM FILE WPIX
ANSWERS '52-61' FROM FILE MEDLINE
ANSWERS '62-65' FROM FILE EMBASE
ANSWERS '66-67' FROM FILE BIOSIS
ANSWER '68' FROM FILE PASCAL
ANSWERS '69-70' FROM FILE BIOENG
ANSWER '71' FROM FILE LIFESCI
ANSWERS '72-73' FROM FILE BIOTECHNO
ANSWERS '74-75' FROM FILE DRUGU
ANSWERS '76-77' FROM FILE DISSABS

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 10:31:51 ON 12 MAY 2006

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 5, 2006 (20060505/UP).

=> d ibib ed ab hitind
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' - CONTINUE? (Y)/N:y

L122 ANSWER 1 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:648348 HCAPLUS
DOCUMENT NUMBER: 141:179552
TITLE: Preparation of **polymerized** **hemoglobin** solutions having reduced amount of **tetramer**
INVENTOR(S): Avella, Anthony; Dewoskin, Richard E.; Doubleday, Marc D.
PATENT ASSIGNEE(S): Northfield Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2004066953	A2	20040812	WO 2004-US2512		20040129	<--
WO 2004066953	A3	20050407				
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI						
AU 2004207595	A1	20040812	AU 2004-207595		20040129	<--
CA 2512169	AA	20040812	CA 2004-2512169		20040129	<--
US 2004186047	A1	20040923	US 2004-767516		20040129	<--
EP 1592437	A2	20051109	EP 2004-706483		20040129	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK						
BR 2004007106	A	20060124	BR 2004-7106		20040129	<--
CN 1741813	A	20060301	CN 2004-80002922		20040129	<--
NO 2005003745	A	20051003	NO 2005-3745		20050804	<--
PRIORITY APPLN. INFO.:			US 2003-443436P	P	20030129	<--
			WO 2004-US2512	W	20040129	

ED Entered STN: 12 Aug 2004
AB A method for producing a substantially **tetramer**-free **Hb** solution is described. The method includes (i) **polymerizing** a solution of **Hb**, (ii) treating the **polymerized Hb** solution to partially degrade the **polymer** to **tetramer**, e.g., by **heating** the **Hb** solution above about 45° for at least 24 h, and (iii) removing **tetramer** from the **Hb** solution by filtration. The Hb may be derived from mammalian blood, such as human or bovine blood.
IC ICM A61K
CC 63-3 (Pharmaceuticals)
ST **Hb** pyridoxalated **polymd tetramer** blood substitute
IT Human
(**Hb** purification from human or bovine blood; preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)
IT Blood
(**Hb** purification from; preparation of **stabilized**

pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT **Hemoglobins**
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PROC (Process)
(carboxyhemoglobins; preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT Blood substitutes
Heat treatment
Oxidation
Quenching (cooling)
Ultrafiltration
(preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT **Hemoglobins**
RL: PUR (Purification or recovery); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT **Hemoglobins**
RL: PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products, with pyridoxal phosphate, **polymerized**; preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT Animal virus
(reduction of; preparation of **stabilized** pyridoxalated **polymd** . **Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT 630-08-0, Carbon monoxide, uses
RL: NUU (Other use, unclassified); USES (Uses)
(atmosphere; preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT 1310-73-2, Sodium hydroxide, uses 7727-37-9, Nitrogen, uses 16940-66-2, Sodium borohydride
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT 54-47-7, Pyridoxal 5-phosphate 111-30-8, Glutaraldehyde 7782-44-7, Oxygen, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT 50-81-7, L-Ascorbic acid, biological studies 50-99-7, D-Glucose, biological studies 72-17-3, Sodium lactate 7447-40-7, Potassium chloride, biological studies 7647-14-5, Sodium chloride, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of **stabilized** pyridoxalated **polymerized Hb** solns. having reduced amount of **tetramer** for blood substitutes)

IT 56-40-6, Glycine, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quenching agent; preparation of **stabilized** pyridoxalated

polymerized Hb solns. having reduced amount of **tetramer** for blood substitutes)

=> d ibib ed ab hitind 2-43
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' - CONTINUE? (Y)/N:y

L122 ANSWER 2 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:243733 HCAPLUS
DOCUMENT NUMBER: 139:32261
TITLE: **Stable** octameric structure of recombinant **hemoglobin** α2β283 Gly→Cys
AUTHOR(S): Fablet, Christophe; Marden, Michael C.; Green, Brian N.; Ho, Chien; Pagnier, Josee; Baudin-Creuza, Veronique
CORPORATE SOURCE: INSERM U 473, Le Kremlin-Bicetre, 94276, Fr.
SOURCE: Protein Science (**2003**), 12(4), 690-695
CODEN: PRCIEI; ISSN: 0961-8368
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 Mar 2003
AB We have engineered a recombinant Hb (rHb βG83C) based on the variant **Hb** Ta-Li, which **oligomerizes** through **intertetramer** disulfide bonds. Size exclusion chromatog. and electrospray ionization mass spectrometry show that the rHb βG83C assembles into an oligomeric structure which is a dimer of tetramers. The oligomer has carbon monoxide-binding properties similar to those of natural human Hb. Unlike HbA, the oligomer does not participate in dimer exchange. The CO kinetics, autoxidn. rate, and gel filtration expts. on the oligomeric βG83C did not show the usual concentration dependence, implying that it does not dissociate easily into smaller species. The octamer could be dissociated by the use of reducing agents. The action of reduced glutathione on oligomeric βG83C exhibited biphasic kinetics for the loss of the octameric form, with a **time** constant for the rapid phase of about 2 h at 1 mM glutathione. However, the size of oligomer βG83C was not modified after incubation with fresh plasma.
CC 6-3 (General Biochemistry)
Section cross-reference(s): 14
IT Molecular association
(**HB**/CO; **stable** octameric structure of recombinant **Hb**)
IT **Hemoglobins**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(human, α2β283 Gly→Cys; **stable** octameric structure of recombinant **Hb**)
IT Globins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(human, β, G83C mutant; **stable** octameric structure of recombinant **Hb**)
IT Quaternary structure
(protein; **stable** octameric structure of recombinant **Hb**)
IT Autoxidation
Blood substitutes

Disulfide group
Human
Protein engineering
(**stable** octameric structure of recombinant **Hb**)
IT 630-08-0, Carbon monoxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**stable** octameric structure of recombinant **Hb**)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 3 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2002:832532 HCAPLUS
DOCUMENT NUMBER: 137:329404
TITLE: Flexible container system for storage of **stabilized hemoglobin** solutions
INVENTOR(S): McGinnis, Robert L.; Chavez, Gabriel; Doubleday, Marc; Dewoskin, Richard; Avella, Anthony
PATENT ASSIGNEE(S): Northfield Laboratories, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085111	A1	20021031	WO 2002-US12118	20020418 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2444590	AA	20021031	CA 2002-2444590	20020418 <--
US 2003065149	A1	20030403	US 2002-124941	20020418 <--
EP 1381274	A1	20040121	EP 2002-723885	20020418 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1516550	A	20040728	CN 2002-812135	20020418 <--
JP 2004538264	T2	20041224	JP 2002-582703	20020418 <--
US 2006014671	A1	20060119	US 2005-231921	20050921 <--
PRIORITY APPLN. INFO.:			US 2001-284651P P	20010418 <--
			US 2002-124941 B1	20020418 <--
			WO 2002-US12118 W	20020418 <--

ED Entered STN: 01 Nov 2002
AB A Hb solution packaged in a flexible oxygen-impermeable container system. The container system includes a multi-layer film having at least a product contact layer, an oxygen and moisture barrier layer and an exterior layer. The flexible container system further includes an interface port for filling the flexible container with the Hb solution and delivering the Hb solution The **Hb** solution comprises a substantially stroma and **tetramer** free, cross linked, pyridoxylated **Hb** solution including preservatives such as ascorbic acid, glycine and dextrose.
IC ICM A01N001-00
ICS A61K038-42
CC 63-3 (Pharmaceuticals)

ST flexible container storage **stability Hb** soln
IT Medical goods
(containers; flexible container system for storage of **stabilized Hb** solns.)
IT **Stability**
(flexible container system for storage of **stabilized Hb** solns.)
IT Polyolefins
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flexible container system for storage of **stabilized Hb** solns.)
IT **Hemoglobins**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flexible container system for storage of **stabilized Hb** solns.)
IT Containers
(medical; flexible container system for storage of **stabilized Hb** solns.)
IT 9002-85-1, Polyvinylidene chloride 9002-88-4, Polyethylene 25067-34-9, Ethylene-vinyl alcohol **copolymer**
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flexible container system for storage of **stabilized Hb** solns.)
IT 50-81-7, Ascorbic acid, biological studies 50-99-7, Dextrose, biological studies 56-40-6, Glycine, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flexible container system for storage of **stabilized Hb** solns.)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 4 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2002:351382 HCAPLUS
DOCUMENT NUMBER: 137:61361
TITLE: Sickle hemoglobin polymer stability probed by triple and quadruple mutant hybrids
AUTHOR(S): Li, Xianfeng; Briehl, Robin W.; Bookchin, Robert M.; Josephs, Robert; Wei, Baoyang; Manning, James M.; Ferrone, Frank A.
CORPORATE SOURCE: Department of Biochemistry, Northeastern University, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (**2002**), 277(16), 13479-13487
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 2002
AB As part of an effort to understand the interactions in HbS polymerization, the authors have produced and studied a recombinant triple mutant, D6A(α)/D75Y(α)/E121R(β), and a quadruple mutant comprising the preceding mutation plus the natural genetic mutation of sickle Hb, E6V(β). These recombinant Hbs expressed in yeast were extensively characterized, and their structure and oxygen binding cooperativity were normal. Their tetramer-dimer dissociation consts. were within a factor of 2 of HbA and HbS. Polymerization of these mutants mixed with

HbS was investigated by a micromethod based on volume exclusion by dextran. The elevated solubility of mixts. of HbS with HbA and HbF in dextran could be accurately predicted without any variable parameters. Relative to HbS, the copolymn. probability of the quadruple mutant/HbS hybrid was 6.2, and the copolymn. probability for the triple mutant/HbS hybrid was 0.52. The pure quadruple mutant had a solubility slightly above that of its hybrid with HbS. One way to explain these results is to require significant cis-trans differences in the polymer and that HbA assemble above 42.5 g/dL. A second way to explain these data is by the modification of motional freedom, thereby changing vibrational entropy in the polymer.

CC 14-6 (Mammalian Pathological Biochemistry)

IT **9035-22-7**, Hb S
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(sickle Hb **polymer stability** probed by triple and quadruple mutant hybrids)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 5 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 15

ACCESSION NUMBER: 1993:78428 HCAPLUS
DOCUMENT NUMBER: 118:78428
TITLE: Effects of β6 amino acid hydrophobicity on **stability** and solubility of **hemoglobin tetramers**
AUTHOR(S): Adachi, K.; Kim, J. Y.; Konitzer, P.; Asakura, T.; Saviola, B.; Surrey, S.
CORPORATE SOURCE: Dep. Pediatr., Child. Hosp. Philadelphia, Philadelphia, PA, 19104, USA
SOURCE: FEBS Letters (**1993**), 315(1), 47-50
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 02 Mar 1993

AB The relationship between different amino acids at the β6 position of **Hb** and **tetramer stability** was studied using a site-directed mutagenesis approach. Precipitation rates during mech. agitation of oxy-Hbs with Gln, Ala, Val, Leu, and Trp at the β6 position increased 2, 5, 13, 21, and 53-**times**, resp., compared with the rate for Hb A. There was a linear relationship between the log of the precipitation rate constant and amino acid hydrophobicity at the β6 position, suggesting that enhanced precipitation of oxy-Hb S during mech. agitation results in part from increased hydrophobicity of β6 Val. Deoxy-Hb solubility increased in the order of β6 Ile, Leu, Val, Trp, Gln, Ala, and Glu, suggesting that hydrophobic interactions between β6 Val and the acceptor site of another **Hb** mol. during deoxy-**Hb** S **polymerization** not only depend on hydrophobicity but also on stereospecificity of the amino acid side chain at the β6 position. Thus, hydrophobic amino acids at the β6 position which promote tetramer instability in the oxy form do not necessarily promote polymerization in the deoxy form.

CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 6

IT **Hemoglobins**
RL: BIOL (Biological study)
(amino acid hydrophobicity in β6 mutants of, solubility and **stability** dependence on)

IT Amino acids, biological studies
RL: PRP (Properties)
(hydrophobicity of side chains of, in **Hb** mutants, **Hb**

solubility and **stability** dependence on)
IT Mutation
(of Hb in β6 position, amino acid side-chain hydrophobicity effects on **Hb** solubility and **stability** in)
IT Hydrophobicity
(of amino acids in β6 mutants of **Hb**, **Hb** solubility and **stability** dependence of)
IT 56-41-7, Alanine, biological studies 56-85-9, Glutamine, biological studies 56-86-0, Glutamic acid, biological studies 61-90-5, Leucine, biological studies 72-18-4, Valine, biological studies 73-22-3, Tryptophan, biological studies 73-32-5, Isoleucine, biological studies
RL: BIOL (Biological study)
(hydrophobicity of side chain of, in **Hb** mutants, **Hb** solubility and **stability** dependence on)
IT 7732-18-5
RL: BIOL (Biological study)
(hydrophobicity, of amino acids in β6 mutants of **Hb**, **Hb** solubility and **stability** dependence of)

L122 ANSWER 6 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 1993:219579 HCAPLUS
DOCUMENT NUMBER: 118:219579
TITLE: **Stabilized hemoglobins** as acellular resuscitative fluids
AUTHOR(S): Cerny, L. C.; Green, A.; Noga, B.; Cerny, E. R.
CORPORATE SOURCE: Utica Coll., Syracuse Univ., Utica, NY, 13502, USA
SOURCE: Biomaterials, Artificial Cells, and Immobilization Biotechnology (**1992**), 20(2-4), 327-30
CODEN: BACBEU; ISSN: 1055-7172
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 May 1993
AB This study reports some recent work dealing with the **stabilization** of the **tetramers** of **Hb**. It is shown that by using a variety of diacids, it is possible to increase the P50 above that of stroma free Hb. In order to lengthen the retention **times** in the circulatory system, the **stabilized Hbs** were complexed with both hydroxyethyl starch **polymers** and polyol tetronic **polymers**. The resulting **Hb-polymer** compds. were then freeze-dried. It was possible to reconstitute the powder by the addition of physiol. saline when needed. The methods presented here appear to be as effective as using pyridoxal phosphate but at a fraction of the cost.
CC 63-3 (Pharmaceuticals)
ST **Hb stabilized** acellular resuscitation; fatty acid **Hb stabilization**; carboxylic acid **Hb stabilization**
IT Blood substitutes and Plasma expanders
(**Hb** reaction products with dicarboxylic acids, **stabilized**)
IT Carboxylic acids, compounds
RL: BIOL (Biological study)
(di-, reaction products, with **Hb**, **stabilized**, as acellular resuscitation fluid)
IT **Hemoglobins**
RL: BIOL (Biological study)
(reaction products, with dicarboxylic acids, **stabilized**, as acellular resuscitation fluid)
IT 77-92-9, Citric acid, biological studies 110-15-6D, Succinic acid, reaction products with **Hb** 110-94-1D, Glutaric acid, reaction

products with **Hb** 124-04-9D, Adipic acid, reaction products with **Hb** 141-82-2D, Malonic acid, reaction products with **Hb** 144-62-7D, Oxalic acid, reaction products with **Hb** 9005-27-0D, Hydroxyethyl starch, reaction products with **Hb** and dicarboxylic acids 110617-70-4D, Tetronic 707, reaction products with **Hb** and dicarboxylic acids 127290-22-6D, Pripol 1009, reaction products with **Hb**
RL: BIOL (Biological study)
(**stabilized**, as acellular resuscitation fluid)

L122 ANSWER 7 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 1993:260762 HCAPLUS
DOCUMENT NUMBER: 118:260762
TITLE: A new type of artificial oxygen carrier: soluble hyperpolymeric hemoglobin with negligible oncotic pressure - production of **thermally stable** hyperpolymers from human blood with glutaraldehyde as cross-linker
AUTHOR(S): Poetzschke, H.; Barnikol, W. K. R.
CORPORATE SOURCE: Inst. Physiol. Pathophysiol., Johannes Gutenberg-Univ. Mainz, Mainz, D-6500, Germany
SOURCE: Biomaterials, Artificial Cells, and Immobilization Biotechnology (**1992**), 20(2-4), 287-91
CODEN: BACBEU; ISSN: 1055-7172
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Jun 1993
AB Hyperpolymers from human Hb were prepared by reduction of Schiff bases, formed from glutaraldehyde and Hb, with NaCNBH3. These stabilized Hb polymers showed no changes in mol. weight distribution, consequently the polymerization index remained the same during incubation up to 10 h.
CC 63-3 (Pharmaceuticals)
IT Blood substitutes and Plasma expanders
(Hb hyperpolymers, preparation of **stable**, glutaraldehyde in)
IT **Hemoglobins**
RL: SPN (Synthetic preparation); PREP (Preparation)
(reaction products, with glutaraldehyde, **polymers**, crosslinked, preparation of **stable**, for blood substitutes)
IT 111-30-8D, Glutaraldehyde, reaction products with Hb, **polymers**, reduced
RL: BIOL (Biological study)
(crosslinked, preparation of **stable**, for blood substitutes)

L122 ANSWER 8 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 18
ACCESSION NUMBER: 1989:463918 HCAPLUS
DOCUMENT NUMBER: 111:63918
TITLE: Pasteurizable, freeze-dryable hemoglobin-based blood substitute
INVENTOR(S): Hsia, Jen Chang
PATENT ASSIGNEE(S): Can.
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 290252	A2	19881109	EP 1988-304059	19880505 <--
EP 290252	A3	19890118		
EP 290252	B1	19930127		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4857636	A	19890815	US 1988-187721	19880429 <--
CA 1306583	A1	19920818	CA 1988-565563	19880429 <--
IL 86258	A1	19941128	IL 1988-86258	19880503 <--
DK 8802428	A	19881106	DK 1988-2428	19880504 <--
DK 174286	B1	20021111		
ZA 8803171	A	19890329	ZA 1988-3171	19880504 <--
AU 8815635	A1	19881110	AU 1988-15635	19880505 <--
AU 610883	B2	19910530		
CN 1030425	A	19890118	CN 1988-103596	19880505 <--
CN 1032471	B	19960807		
AT 84970	E	19930215	AT 1988-304059	19880505 <--
ES 2053729	T3	19940801	ES 1988-304059	19880505 <--
JP 63297330	A2	19881205	JP 1988-109257	19880506 <--
JP 05032372	B4	19930514		
US 5189146	A	19930223	US 1991-781671	19911024 <--
US 5364932	A	19941115	US 1992-918610	19920727 <--
PRIORITY APPLN. INFO.:			GB 1987-10598	A 19870505 <--
			US 1988-187721	A3 19880429 <--
			EP 1988-304059	A 19880505 <--
			US 1989-359396	B1 19890531 <--
			US 1991-781671	A3 19911024 <--

OTHER SOURCE(S): MARPAT 111:63918

ED Entered STN: 20 Aug 1989

AB A process is given, by which a blood substitute (HemoSafe) is derived from uniformly-stabilized monomers and polymers of deoxyHb in its tight (T) conformation, with O affinity similar to that of human blood. HemoSafe is derived from Hb of animals or humans. HemoSafe (animal) differs from HemoSafe (human) in that it is free of polymers in order to reduce potential immunogenicity if used in man. The stabilized deoxyHbs are converted to their carbonmonoxy derivs. (CO-HeoSafe) which are then stable under pasteurization conditions to render them viral disease transmission-free. CO-HemoSafes are stable for 2 mo at 56° either in solution or the freeze-dried state. For transfusion CO-HemoSafes are easily oxygenated under sterile conditions by photoconversion yielding oxy-HemoSafe. A transfusable Met-Hb derivative for treatment of cyanide poisoning, is derived by converting oxy-HemoSafe to Met-HemoSafe. A 1% solution of human oxy-Hb (R) in 0.1M phosphate buffer (pH 8) (350 mL) was converted into deoxy-Hb (T) under vacuum followed by the addition of 0.1 mmol Na dithionite in 0.3 mL buffer and of 1.08 mmol periodate-oxidized ring-opened raffinose in 20 mL buffer and, after 4 h, of 15 mmol NaBH4 in 5 mL 1 mM NaOH. CO was bubbled into the reaction mixture, followed by pasteurization (60° for 10 h) and lyophilization, to give CO-HemoSafe I (T).

IC ICM A61K037-14

CC 63-3 (Pharmaceuticals)

ST **Hb stabilized** blood substitute

IT **Hemoglobins, carbonyl-**
RL: PREP (Preparation)
(**stabilized**, preparation of, as storable blood substitute precursor)

IT **Hemoglobins, met-**
RL: PREP (Preparation)
(**stabilized**, preparation of, for cyanide scavenging)

IT Blood substitutes and Plasma expanders
(**tetrameric Hbs**, conformationally **stabilized**)

IT **Hemoglobins**
RL: BIOL (Biological study)
(**tetramers**, conformationally **stabilized**, as blood substitutes)
IT Carbohydrates and Sugars, biological studies
RL: BIOL (Biological study)
(aldehydes, **Hb stabilization** by, as blood substitute)
IT Aldehydes, biological studies
RL: BIOL (Biological study)
(di-, **Hb stabilization** by, as blood substitute)
IT Aldehydes, **polymers**
RL: BIOL (Biological study)
(di-, **polymers**, **Hb stabilization** by, as blood substitute)
IT 57-50-1D, periodate-oxidized 111-30-8, Pentanedial 512-69-6D, Raffinose, periodate-oxidized 9005-80-5D, Inulin, periodate-oxidized
RL: BIOL (Biological study)
(**Hb stabilization** by, as blood substitute)

L122 ANSWER 9 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 19
ACCESSION NUMBER: 1981:543884 HCAPLUS
DOCUMENT NUMBER: 95:143884
TITLE: Chemical modification of human hemoglobin by antisickling concentrations of nitrogen mustard
AUTHOR(S): Roth, Eugene F., Jr.; Arnone, Arthur; Bookchin, Robert M.; Nagel, Ronald L.
CORPORATE SOURCE: Dep. Med., Albert Einstein Coll. Med., Bronx, NY, USA
SOURCE: Blood (**1981**), 58(2), 300-8
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB In in vitro alkylation of human Hb A [**9034-51-9**], S [**9035-22-7**] and H [9034-79-1], nirogen mustard (HN2) [55-86-7] was examined Two types of adducts are formed: alkali labile adducts, which are mostly esterified carboxyl groups easily removed by dialysis against weakly alkaline solns., and **stable** alkali-resistant adducts. The **stable** adducts, which are responsible for the inhibition of **polymerization** of deoxy-**HbS**, do not alter the isoelec. point of **Hb**. Higher pHs enhance the binding of HN2 to Hb as does the deoxy conformation. Separation of α and β globin chains revealed that >90% of 14C-HN2 is bound in a **stable** manner to β chains; however, peptide mapping did not yield a ninhydrin-pos., radioactive peptide because of elution of the label during this procedure. There was also evidence that about 25% of the rapidly titratable-SH group of HbA and HbS were reacted with HN2. X-ray crystallog. study of HbA crystals revealed that β histidines 97, 117, and 143 were reacted with HN2. In addition, the β chain N terminus (the location of the β 6 Val substitution in HbS) was displaced but not alkylated. By means of gelation studies with deoxy-HbS, it was found that alkylation of β S chains inhibited gelation, whereas alkylation of α chains was without effect. Moreover, raising the pH during the HN2 reaction (but not during the gelation study) enhanced the inhibitory effect of HN2 on gelation. A plot of the min. gelation concentration as a function of the pH during alkylation produced a curve that closely resembled the titration of a group with a pK near 7. This is a consistent with alkylation of a histidine imidazole group. Apparently the **stable** adducts of HN2 and **Hb** consist mainly of histidine adducts with some involvement of -SH groups from the β 93 cysteine. In addition, the antisickling

properties of HN2 are likely due to the alkylation of the β 2 and β 117 histidine residues that reside in the **intertetrameric** contact areas of the deoxy-**HbS polymer.**
CC 1-4 (Pharmacodynamics)

L122 ANSWER 10 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:321740 HCAPLUS
DOCUMENT NUMBER: 143:323259
TITLE: Hemoglobinopathies due to structural mutations
AUTHOR(S): Nagel, Ronald L.
CORPORATE SOURCE: Division of Hematology, Albert Einstein College of Medicine, Bronx, New York, NY, 10461, USA
SOURCE: Molecular Hematology (2nd Edition) (2005), 159-172. Editor(s): Provan, Drew; Gribben, John G. Blackwell Publishing Ltd.: Oxford, UK.
CODEN: 69GTKW; ISBN: 1-4051-1255-7
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
ED Entered STN: 15 Apr 2005
AB A review discusses the hemoglobinopathies that are caused by mutations in the exon portion of the α or β globin genes, focusing on the most frequent mutations that must be considered in the differential diagnosis of the common hemoglobinopathies.
CC 14-0 (Mammalian Pathological Biochemistry)
IT **Hemoglobins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(hemoglobinopathy is caused by Hb mol. alteration like change in O2 affinity, heme environment, **stability**, creation of new property like **polymerization**, crystallization, microcytosis due to mutation in structural genes in human)
IT **Hemoglobins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic disorders, hemoglobinopathy; hemoglobinopathy is caused by Hb mol. alteration like change in O2 affinity, heme environment, **stability**, creation of new property like **polymerization**, crystallization, microcytosis due to mutation in structural genes in human)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 11 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:169983 HCAPLUS
DOCUMENT NUMBER: 138:210324
TITLE: Preparation of total nutrient admixtures as stable multicomponent liquids or dry powders
INVENTOR(S): Magdassi, Shlomo; Yang, Andrew; Tao, Chunlin; Desai, Neil P.; Yao, Zhiwen; Soon-Shiong, Patrick
PATENT ASSIGNEE(S): American Bioscience, Inc., USA
SOURCE: U.S., 7 pp., Cont.-in-part of U.S. 5,560,933.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 19
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6528067	B1	20030304	US 1999-457085	19991207 <--
US 5439686	A	19950808	US 1993-23698	19930222 <--

US 5560933	A	19961001	US 1995-412726	19950329 <--
PRIORITY APPLN. INFO.:			US 1993-23698	A3 19930222 <--
			US 1995-412726	A2 19950329 <--

ED Entered STN: 06 Mar 2003

AB Stabilized total nutrient admixt. (TNA) compns., useful for the in vivo parenteral delivery of pharmacol. acceptable lipids or fats, as well as methods for their preparation are described. In particular, the pharmacol. acceptable lipid or fat is contained within a biocompatible polymer, e.g., a protein, walled shell. In a particular embodiment of the invention, a TNA composition using human serum albumin (HSA) as a stabilizer has been prepared as a convenient three-in-one formulation (i.e., containing a fat emulsion, dextrose, and amino acids plus electrolytes). This "three-in-one" formulation can be prepared in liquid form or in dry form (comprising submicron-sized nanoparticles). The dried material is stable, even under long term storage, and is easily reconstituted immediately before use by simply adding sterile water (with or without vitamin supplementation). This serves to rehydrate the powder into a TNA suitable for injection. The long shelf life, ease of reconstitution, and single-component injectability of invention compns. provide significant cost savings, as such compns. can be reconstituted and administered safely, even at home. In addition, HSA, the stabilizing agent of choice for use in the practice of the present invention, has been shown to improve survival and wellness when given as a supplement to patients receiving conventional forms of total nutrient admixts.

IC ICM A61K039-02
ICS A61K009-14; C08J009-28

INCL 424264000; 424489000; 521065000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 18

IT Amino acids, biological studies
Antibodies and Immunoglobulins
Carbohydrates, biological studies
Fats and Glyceridic oils, biological studies
Fibrinogens
Fibronectins
Hemoglobins
Lipids, biological studies
Nucleic acids
Polysaccharides, biological studies
Vitronectin
RL: FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of **stabilized** total nutrient admixts. as multicomponent liqs. or dry powders using **polymer stabilizers**)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 12 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2001:573556 HCAPLUS
DOCUMENT NUMBER:	135:157660
TITLE:	Method for preserving a hemoglobin blood substitute
INVENTOR(S):	Gawryl, Maria S.; Houtchens, Robert A.; Light, William R.
PATENT ASSIGNEE(S):	Biopure Corporation, USA
SOURCE:	U.S., 20 pp., Cont.-in-part of U.S. Ser. No. 974,658, abandoned. CODEN: USXXAM
DOCUMENT TYPE:	Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 6271351	B1	20010807	US 1998-173189	19981014	<--
US 5854209	A	19981229	US 1995-409337	19950323	<--
US 5840852	A	19981124	US 1995-458916	19950602	<--
US 5691452	A	19971125	US 1995-471583	19950607	<--
US 6288027	B1	20010911	US 1999-348881	19990707	<--
US 6610832	B1	20030826	US 1999-349290	19990707	<--
CA 2346466	AA	20000420	CA 1999-2346466	19991013	<--
WO 2000021366	A1	20000420	WO 1999-US23631	19991013	<--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9964249	A1	20000501	AU 1999-64249	19991013	<--
AU 743248	B2	20020124			
EP 1121016	A1	20010808	EP 1999-951910	19991013	<--
EP 1121016	B1	20030115			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002527360	T2	20020827	JP 2000-575363	19991013	<--
AT 230924	E	20030215	AT 1999-951910	19991013	<--
NZ 511008	A	20030228	NZ 1999-511008	19991013	<--
ES 2186418	T3	20030501	ES 1999-951910	19991013	<--
US 2002128182	A1	20020912	US 2001-912254	20010724	<--
US 7041800	B1	20060509	US 2002-18599	20020522	<--
US 7041799	B1	20060509	US 2002-18529	20020603	<--
PRIORITY APPLN. INFO.:			US 1995-409337	A1 19950323	<--
			US 1995-458916	A2 19950602	<--
			US 1995-471583	A1 19950607	<--
			US 1997-974658	B2 19971119	<--
			US 1998-173189	A2 19981014	<--
			US 1999-348881	A1 19990707	<--
			US 1999-349290	A1 19990707	<--
			WO 1999-US23631	W 19991013	<--
			WO 2000-US18747	W 20000707	<--
			WO 2000-US18750	W 20000707	<--

ED Entered STN: 08 Aug 2001
AB A method for preserving the stability of a Hb blood substitute comprises maintaining the Hb blood substitute in an atmospheric substantially free of oxygen. The invention also involves a method for producing a stable polymerized Hb blood-substitute from blood. The method of this invention includes mixing blood with an anticoagulant to form a blood solution, washing the red blood cells in the blood solution and then separating the washed red blood cells from the white blood cells. This method also includes disrupting the red blood cells to release Hb and form a Hb solution, which is then treated by high performance liquid chromatog. to form a Hb eluate. The Hb eluate is then deoxygenated, contacted with a first sulfhydryl compound to form an oxidation-stabilized deoxygenated Hb solution, and mixed with a crosslinking agent to form a polymerization reaction mixture, which is then polymerized

The polymerized Hb solution is then diafiltered with a physiol. solution and with a sulfhydryl compound, whereby the polymerized Hb solution is made physiol. acceptable, and whereby the sulfhydryl compound scavenges oxygen, to form a stable polymerized Hb blood substitute, which is then packaged and stored in an atmospheric substantially free of oxygen.

IC ICM C07K014-805
ICS A61B019-02
INCL 530385000
CC 63-3 (Pharmaceuticals)
IT **Hemoglobins**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crosslinked, **polymerized**; preparation and preservation of **stable** Hb blood substitutes in atmospheric free of oxygen)
IT **Hemoglobins**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preparation and preservation of **stable** Hb blood substitutes in atmospheric free of oxygen)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 13 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:101593 HCAPLUS
DOCUMENT NUMBER: 134:277085
TITLE: Hemoglobin of the Antarctic Fishes Trematomus bernacchii and Trematomus newnesi: Structural Basis for the Increased **Stability** of the Liganded **Tetramer** Relative to Human Hemoglobin
AUTHOR(S): Giangiacomo, Laura; D'Avino, Rossana; di Prisco, Guido; Chiancone, Emilia
CORPORATE SOURCE: Department of Biochemical Sciences A. Rossi Fanelli, CNR Center of Molecular Biology University of Rome La Sapienza, Rome, 00185, Italy
SOURCE: Biochemistry (**2001**), 40(10), 3062-3068
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Feb 2001
AB Hbs extracted from fishes that live in temperate waters show little or no dissociation even in the liganded form, unlike human Hb (HbA). To establish whether cold adaptation influences the tendency to dissociate, the dimer-tetramer association consts. (L2,4) of the carbonmonoxy derivs. of representative Hbs from two Antarctic fishes, Trematomus newnesi (Hb1Tn) and Trematomus bernacchii (Hb1Tb), were determined by anal. ultracentrifugation as a function of pH in the range 6.0-8.6 and compared to. HbA. HbA is more dissociated than fish Hbs at all pH values and in particular at pH 6.0. In contrast, both fish Hbs are mostly tetrameric over the whole pH range studied. The extent of hydrophobic surface area buried at the $\alpha 1\beta 2$ interface upon association of dimers into tetramers and the number of hydrogen bonds formed are currently thought to play a major role in the stabilization of the Hb tetramer. These contributions were derived from the x-ray structures of the three Hbs under study and found to be in good agreement with the exptl. determined L2,4 values. PH affects oxygen binding of T. bernacchii and T. newnesi Hbs in a different fashion. The lack of a pH effect on the dissociation of the liganded proteins supports the proposal that the structural basis of such effects resides in the T (unliganded) structure rather than in the R (liganded) one.

CC 6-3 (General Biochemistry)
Section cross-reference(s): 12
ST Hb antarctic fish Trematomus liganded **tetramer stability**
IT Hydrophobicity
(hydrophobic interphase between Hb subunits; structural basis for increased **stability** of liganded **tetramer** of Hbs of antarctic fishes Trematomus bernacchii and Trematomus newnesi)
IT Conformation
Quaternary structure
(protein; structural basis for increased **stability** of liganded **tetramer** of Hbs of antarctic fishes Trematomus bernacchii and Trematomus newnesi)
IT Fish
Formation constant
Hydrogen bond
Molecular association
Temperature adaptation, animal
Trematomus bernacchii
Trematomus newnesi
pH
(structural basis for increased **stability** of liganded **tetramer** of Hbs of antarctic fishes Trematomus bernacchii and Trematomus newnesi)
IT **Hemoglobins**
RL: PRP (Properties)
(structural basis for increased **stability** of liganded **tetramer** of Hbs of antarctic fishes Trematomus bernacchii and Trematomus newnesi)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 14 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:494160 HCAPLUS
DOCUMENT NUMBER: 133:227678
TITLE: In vitro and in vivo stability of polymerized mixed liposomes composed of 2,4-octadecadienoyl groups of phospholipids
AUTHOR(S): Akama, Kazuhiro; Awai, Kouji; Yano, Yoshihiro; Tokuyama, Satoru; Nakano, Yoshio
CORPORATE SOURCE: Tsukuba Research Laboratory, NOF Corporation, Tsukuba, 300-2635, Japan
SOURCE: Polymers for Advanced Technologies (**2000**), 11(6), 280-287
CODEN: PADTE5; ISSN: 1042-7147
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Jul 2000
AB The in vitro stability, under freeze-thawing procedures, and in vivo degradation, in rat spleen, of two types of polymerized liposomes were examined:
1,2-bis-[(2E,4E)-octadecadienoyl]-sn-glycero-3-phosphocholine (DODPC) and 1-acyl-2-[(2E,4E)-octadecadienoyl]-sn-glycero-3-phosphocholine (AODPC) were used as polymerizable phospholipids. The lipid composition of the liposomes was prepared as DODPC/Chol/SA (Chol = cholesterol, SA = stearic acid), AODPC/Chol/SA (7/7/2 by molar ratio), AODPC/DPPC/Chol/SA (3.5/3.5/7/2 by molar ratio). The liposomes were extruded through a 0.2 μm polycarbonate- filter to obtain the approx. particle size of 0.2 μm, and then irradiated with γ-rays. Hb-encapsulated liposomes were also prepared in the same manner with concentrated Hb solution The

DODPC/Chol/SA liposome exhibited no trace of particle size change nor Hb leakage. Although not as excellent as the former, the AODPC-base liposome showed slightly diameter change (below 7.5%) with a substantial abatement of Hb leakage (<3.5%). Transmission electron microscopy observation of spleens also revealed more efficient degradability with AODPC/DPPC/Chol/SA liposome than with DODPC/Chol/SA liposome. Hb-encapsulated AODPC/DPPC/Chol/SA liposome, after five freeze-thawing cycles, attained an Hb leakage below 3.5% with a particle size change of 0.7-7.5%, and reduced the spleen retention compared with the DODPC-base liposome. These results suggest that AODPC/DPPC/Chol/SA liposome can be used as a longterm preservable blood substitute.

CC 63-6 (Pharmaceuticals)

IT **Hemoglobins**
Lysophosphatidylcholines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro and in vivo **stability** of **polymerized** mixed liposomes composed of octadecadienoyl groups of phospholipids)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 15 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:606982 HCAPLUS
DOCUMENT NUMBER: 131:233534
TITLE: Method for producing a stable polymerized hemoglobin blood-substitute
INVENTOR(S): Rausch, Carl W.; Gawryl, Maria S.; Houtchens, Robert A.; Laccetti, Anthony J.; Light, William R.
PATENT ASSIGNEE(S): Biopure Corporation, USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. 5,618,919.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5955581	A	19990921	US 1995-484775	19950607 <--
CA 1312009	A1	19921229	CA 1987-551356	19871109 <--
US 5084558	A	19920128	US 1987-119121	19871110 <--
AT 74274	E	19920415	AT 1987-116556	19871110 <--
US 5296465	A	19940322	US 1992-820153	19920113 <--
US 5618919	A	19970408	US 1994-209949	19940311 <--
US 5854209	A	19981229	US 1995-409337	19950323 <--
US 5840852	A	19981124	US 1995-458916	19950602 <--
US 5753616	A	19980519	US 1995-478004	19950607 <--
CA 2215697	AA	19960926	CA 1996-2215697	19960322 <--
WO 9629346	A1	19960926	WO 1996-US4030	19960322 <--
W: AU, CA, JP, NZ				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9653227	A1	19961008	AU 1996-53227	19960322 <--
AU 705225	B2	19990520		
EP 815138	A1	19980107	EP 1996-909855	19960322 <--
EP 815138	B1	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11502821	T2	19990309	JP 1996-528657	19960322 <--
NZ 305258	A	20001027	NZ 1996-305258	19960322 <--
EP 1094078	A2	20010425	EP 2000-204276	19960322 <--
EP 1094078	A3	20010502		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

EP 1093720	A1	20010425	EP 2000-204281		19960322 <--
EP 1094079	A2	20010425	EP 2000-204284		19960322 <--
EP 1094079	A3	20010502			
EP 1211261	A2	20020605	EP 2002-75127		19960322 <--
EP 1211261	A3	20040317			
AT 222926	E	20020915	AT 1996-909855		19960322 <--
PT 815138	T	20021231	PT 1996-909855		19960322 <--
ES 2179188	T3	20030116	ES 1996-909855		19960322 <--
US 5905141	A	19990518	US 1997-838514		19970408 <--
US 6506725	B1	20030114	US 1999-309069		19990510 <--
PRIORITY APPLN. INFO.:			US 1986-928345	B2	19861110 <--
			US 1987-107421	B2	19871013 <--
			US 1987-119121	A1	19871110 <--
			US 1992-820153	A1	19920113 <--
			US 1994-209949	A2	19940311 <--
			US 1995-409337	A1	19950323 <--
			US 1995-458916	A2	19950602 <--
			EP 1987-116556	A	19871110 <--
			US 1995-471583	A	19950607 <--
			US 1995-473497	A	19950607 <--
			US 1995-478004	A	19950607 <--
			US 1995-484775	A3	19950607 <--
			US 1995-487288	A	19950607 <--
			EP 1996-909855	A3	19960322 <--
			WO 1996-US4030	W	19960322 <--
			US 1997-838514	A1	19970408 <--

ED Entered STN: 24 Sep 1999

AB A method for producing a stable polymerized Hb blood-substitute from blood. The method of this invention includes mixing blood with an anticoagulant to form a blood solution, washing the red blood cells in the blood solution and then separating the washed red blood cells from the white blood cells. This method also includes disrupting the red blood cells to release Hb and form a Hb solution, which is then treated by high performance liquid chromatog. to form a Hb eluate. The Hb eluate is then deoxygenated, contacted with a first sulfhydryl compound to form an oxidation-stabilized deoxygenated Hb solution, and mixed with a crosslinking agent to form a polymerization reaction mixture, which is then polymerized The polymerized Hb solution is then diafiltered with a physiol. solution and with a sulfhydryl compound, whereby the polymerized Hb solution is made physiol. acceptable, and whereby the sulfhydryl compound scavenges oxygen, to form a stable polymerized Hb blood-substitute. A stable polymerized Hb was prepared according to above method and was used sodium citrate as anticoagulant and glutaraldehyde as the crosslinking agent. The efficacy and tolerance of increasing rates of i.v. administration of Hb blood substitute upon hemodynamic, neuroendocrine and hematol. parameters in humans was studied.

IC ICM C07K014-805

INCL 530385000

CC 63-3 (Pharmaceuticals)

IT **Hemoglobins**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**polymerized**; method for producing **stable** **polymerized** Hb blood-substitute)
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 16 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:273581 HCAPLUS
DOCUMENT NUMBER: 130:301675
TITLE: Preparation of a **polymerized** **hemoglobin** for a **stable** blood substitute
INVENTOR(S): Light, William R.; Gawryl, Maria S.; Laccetti, Anthony J.
PATENT ASSIGNEE(S): Biopure Corporation, USA
SOURCE: U.S., 15 pp., Cont.-in-part of U.S. 5,840,852.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5895810	A	19990420	US 1995-487288	19950607 <--
US 5854209	A	19981229	US 1995-409337	19950323 <--
US 5840852	A	19981124	US 1995-458916	19950602 <--
CA 2215697	AA	19960926	CA 1996-2215697	19960322 <--
AU 9653227	A1	19961008	AU 1996-53227	19960322 <--
AU 705225	B2	19990520		
EP 815138	A1	19980107	EP 1996-909855	19960322 <--
EP 815138	B1	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11502821	T2	19990309	JP 1996-528657	19960322 <--
NZ 305258	A	20001027	NZ 1996-305258	19960322 <--
EP 1094078	A2	20010425	EP 2000-204276	19960322 <--
EP 1094078	A3	20010502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1093720	A1	20010425	EP 2000-204281	19960322 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1094079	A2	20010425	EP 2000-204284	19960322 <--
EP 1094079	A3	20010502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1211261	A2	20020605	EP 2002-75127	19960322 <--
EP 1211261	A3	20040317		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 222926	E	20020915	AT 1996-909855	19960322 <--
PT 815138	T	20021231	PT 1996-909855	19960322 <--
ES 2179188	T3	20030116	ES 1996-909855	19960322 <--
PRIORITY APPLN. INFO.:			US 1995-409337	A1 19950323 <--
			US 1995-458916	A2 19950602 <--
			US 1995-471583	A 19950607 <--
			US 1995-473497	A 19950607 <--
			US 1995-478004	A 19950607 <--

US 1995-484775	A	19950607	<--
US 1995-487288	A	19950607	<--
EP 1996-909855	A3	19960322	<--
WO 1996-US4030	W	19960322	<--

ED Entered STN: 04 May 1999

AB A composition of matter comprising a **stable polymerized Hb** solution, useful for forming blood-substitutes, and a method for forming said **stable polymerized Hb** solution is disclosed. The **stable polymerized Hb** solution, and derived blood-substitutes, of this invention comprise **polymerized Hb** and a sulfhydryl compound, both in solution, wherein the sulfhydryl compound **stabilizes** the **polymerized Hb.** The method of this invention comprises deoxygenating Hb in a Hb solution and then mixing the deoxygenated **Hb** with a sulfhydryl compound to form an oxidation-**stabilized**, deoxygenated **Hb** solution Subsequently, the oxidation-**stabilized** deoxygenated **Hb** solution is mixed with a crosslinking agent to form a **polymerization** reaction mixture, which is then **polymerized** to form a **stable polymerized Hb** solution Using N-acetyl cysteine and glutaraldehyde a **polymerized Hb** was prepared according to above method. Anal. of **polymerized Hb** solution showed that 96% or more of the **Hb** mols. were intermolecularly and/or intramolecularly cross-linked, with 28-33% of the poly(**Hb**) being in a intramolecularly cross-linked **tetrameric** form and about 4-7% of the poly(**Hb**) had a mol. weight greater than 500,000 Dalton. The **polymerized Hb** blood-substitute produced according to the method of this invention was stable for two years at room **temp** . with only minium changes in the composition of the blood-substitute.

IC ICM C07K014-805

INCL 530385000

CC 63-3 (Pharmaceuticals)

ST **stable polymd Hb** blood substitute prepn

IT Water purification
(deoxygenation; preparation of **polymerized Hb** for **stable** blood substitute)

IT Blood substitutes
Crosslinking agents
Reducing agents
(preparation of **polymerized Hb** for **stable** blood substitute)

IT **Hemoglobins, oxyhemoglobins**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(preparation of **polymerized Hb** for **stable** blood substitute)

IT **Hemoglobins**
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation of **polymerized Hb** for **stable** blood substitute)

IT Dialdehydes
Thiols (organic), reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **polymerized Hb** for **stable** blood substitute)

IT 59-52-9, 2,3-Dimercapto-1-propanol 68-11-1, reactions 70-18-8, Glutathione, reactions 111-30-8, Glutaraldehyde 616-91-1, N-Acetyl-L-cysteine 636-58-8, γ-Glutamyl-cysteine 1191-08-8, 1,4-Butanedithiol 3374-22-9, Cysteine 16940-66-2, Sodium borohydrate
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of **polymerized Hb** for **stable** blood substitute)
IT 72-17-3, Sodium lactate 996-31-6, Potassium lactate 7647-14-5, Sodiumchloride, biological studies 10043-52-4, Calciumchloride, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of **polymerized Hb** for **stable** blood substitute)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 17 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:672950 HCAPLUS
DOCUMENT NUMBER: 132:8923
TITLE: Stabilization of the T-state of ferrous human adult hemoglobin by chlorpromazine and trifluoperazine
AUTHOR(S): Ascenzi, Paolo; Bertollini, Alberto; Coletta, Massimo; Lucacchini, Antonio
CORPORATE SOURCE: Department of Biology, University of Rome, Rome, I-00146, Italy
SOURCE: Biotechnology and Applied Biochemistry (**1999**), 30(2), 185-187
CODEN: BABIEC; ISSN: 0885-4513
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Oct 1999
AB In the present study, the effect of the neuroleptics chlorpromazine (2-chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine) and trifluoperazine {10-[3-(4-methylpiperazin-1-yl)-propyl]-2-(trifluoromethyl)-10H-phenothiazine} on the EPR-spectroscopic properties of ferrous human adult nitrosylated Hb (HbNO) is reported. Addition of the two drugs to HbNO shifted the conformational equilibrium from the high- to the low-affinity form of the ligated tetramer, as observed for 2,3-D-glycerate bisphosphate, the physiol. modulator of Hb action. The effect of chlorpromazine and trifluoperazine on the EPR-spectroscopic properties of HbNO was enhanced by inositol hexakisphosphate. The binding of neuroleptics to ferrous human adult Hb may represent an important undesirable side effect. In fact, oxygen affinity for ferrous human adult Hb decreases on increasing chlorpromazine and trifluoperazine concentration In addition, red blood cells may act as neuroleptic scavengers.
CC 1-11 (Pharmacology)
IT **Hemoglobins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitrosylHbs; **stabilization** of **tetramer** state of ferrous human adult Hb by chlorpromazine and trifluoperazine)
IT **Hemoglobins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**stabilization** of **tetramer** state of ferrous human adult Hb by chlorpromazine and trifluoperazine)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 18 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:358202 HCAPLUS
DOCUMENT NUMBER: 129:106082
TITLE: **Thermal stability** and electron transfer reaction of PEO-modified hemoglobin cast on

an ITO electrode in **polymer** electrolytes
AUTHOR(S): Kawahara, Natsue Y.; Ohno, Hiroyuki
CORPORATE SOURCE: Department of Biotechnology, Tokyo University of Agriculture and Technology, Tokyo, 184, Japan
SOURCE: Electrochimica Acta (**1998**), 43(10-11), 1493-1497
CODEN: ELCAAV; ISSN: 0013-4686
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 13 Jun 1998
AB Poly(ethylene oxide)-modified human Hb (PEO-Hb) was cast on the indium tin oxide (ITO) glass electrode from aqueous solution, and the dried electrode was soaked into salt-containing PEO oligomers (MW:400, 600, 1000). Their redox reaction was investigated with both cyclic voltammetry and UV-vis spectrophotometry at wide **temperature** from 30 to 160°. The electron transfer reactions of PEO-Hb cast on the ITO glass electrode were clearly detected in PEO oligomer (MW:400) at **temps.** from 30 to 140° with cyclic voltammetry. The extraordinary **thermal** stability of PEO-Hb on the ITO glass electrode was observed in only PEO oligomers as a solvent which was never seen in buffer solution The **thermal** stability was improved by increasing the mol. weight of solvent PEO. The absorbance at Soret band for PEO-Hb was quite stable for 10 h at 80° in PEO1000 (MW:1000). PEO-Hb on the ITO glass electrode was also stable for 3 h at 120°, but denatured gradually at 140° in PEO1000.
CC 9-1 (Biochemical Methods)
ST **thermal stability** electron transfer reaction; PEO Hb ITO electrode **polymer** electrolyte
IT **Hemoglobins**
RL: DEV (Device component use); USES (Uses)
(PEO-modified; **thermal stability** and electron transfer reaction of PEO-modified Hb cast on ITO electrode in **polymer** electrolytes)
IT Electron transfer
Glass electrodes
Thermal stability
(**thermal stability** and electron transfer reaction of PEO-modified Hb cast on ITO electrode in **polymer** electrolytes)
IT Polyoxyalkylenes, uses
RL: DEV (Device component use); USES (Uses)
(**thermal stability** and electron transfer reaction of PEO-modified Hb cast on ITO electrode in **polymer** electrolytes)
IT 25322-68-3, Poly(ethylene oxide) 50926-11-9, Indium tin oxide
RL: DEV (Device component use); USES (Uses)
(**thermal stability** and electron transfer reaction of PEO-modified Hb cast on ITO electrode in **polymer** electrolytes)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 19 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:757960 HCAPLUS
DOCUMENT NUMBER: 130:120365
TITLE: hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way
AUTHOR(S): Kober, Ingo; Teichmann, Martin; Seifart, Klaus H.

CORPORATE SOURCE: Institut fur Molekularbiologie und Tumorforschung, Marburg, D-35033, Germany
SOURCE: Journal of Molecular Biology (**1998**), 284(1), 7-20
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 03 Dec 1998

AB It has been shown that under specific conditions, transcription of protein coding genes can be efficiently initiated by RNA polymerase (pol) III in vitro. We examined the formation and composition of such pol III transcription complexes on the duck histone H5 and αA-globin promoters and found that the essential step for the formation of pol III transcription complexes on these pol II promoters was the stable binding of transcription factor (TF) IIIB-β. For this process, the intact TFIIIB-β complex, consisting of TBP and associated factors (TAFs) was needed and the prior association of pol III assembly factors was not necessary. We demonstrate for the first **time** that hTFIIIB-β alone is able to bind to pol II promoter DNA. This resulted in a very stable complex which was resistant to high concns. of heparin. Although immunodepletion revealed that TBP is essentially required for complex formation, other components of hTFIIIB-β must also be involved, since TBP itself is unable to form heparin-resistant complexes and does not mediate pol III commitment per se. pol III is recruited to these pol II promoters in a strictly TFIIIC1 dependent way. After binding of TFIIIB-β, the addition of TFIIIC1 and pol III were sufficient to yield productive pol III transcription complexes, which utilized the correct pol II initiation site. From these findings, we postulate that TFIIIC1 is involved in the recruitment of pol III and may thus form a bridge between TFIIIB-β and the enzyme. This finding provides the first evidence for functional contacts between TFIIIC1 and pol III, which could be of general importance for the assembly of pol III transcription complexes. (c) 1998 Academic Press.

CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 6, 13

ST TFIIIBbeta binds **polymerase** II promoters recruits **polymerase** III TFIIIC1

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(GFI, intact TFIIIB-β complex, consisting of TBP and associated factors (TAFs) was needed; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(TATA box-binding, intact TFIIIB-β complex, consisting of TBP and associated factors (TAFs) was needed; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(TFIIIB (transcription factor IIIB), TFIIIB-β; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(TFIIIC (transcription factor IIIC), TFIIIC1; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Duck
(formation and composition of pol III transcription complexes on duck histone H5 and αA-globin promoters; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Promoter (genetic element)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tsp (transcription start point), after binding of TFIIIB-β, TFIIIC1 and pol III were sufficient to yield pol III transcription complexes, utilizing pol II initiation site; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III by hTFIIIC1)

IT **Hemoglobins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αA-globin, formation and composition of pol III transcription complexes on duck histone H5 and αA-globin promoters; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

IT 9014-24-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(II; hTFIIIB-β **stably** binds to pol II promoters and recruits RNA **polymerase** III in a hTFIIIC1 dependent way)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 20 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:547433 HCAPLUS
DOCUMENT NUMBER: 127:230705
TITLE: **Thermodynamic stability** of the asymmetric doubly-ligated hemoglobin **tetramer** (α+CNβ+CN)(αβ): methodological and mechanistic issues
AUTHOR(S): Ackers, Gary K.; Perrella, Michele; Holt, Jo M.; Denisov, Ilya; Huang, Yingwen
CORPORATE SOURCE: Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO, 63110, USA
SOURCE: Biochemistry (**1997**), 36(36), 10822-10829
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 28 Aug 1997
AB Free energy contributions to cooperativity by the eight ligation intermediates of human Hb have been characterized extensively using six oxygenation analogs [cf. Huang et al. (1996) Biophys. J. 71, 2094-2105]. These unprecedented data bases have strongly supported the mol. code mechanism of Hb cooperativity [Ackers et al. (1992) Science 255, 54-83]. The present study addresses a recent argument against this work [Shibayama

et al. (1997) Biochem. 36, 4375-4381] based on "free energy" detns. for a doubly-ligated species of the CN-met analog. Shibayama et al. (1997) have claimed that, in the hybridization expts. that have been used to determine free energy of the asym. "species [21]" tetramer, a portion of the bound cyanide is allegedly released from CN-met Hb during the incubation with deoxy Hb that is used to achieve hybrid equilibrium These authors have claimed that cyanide release has resulted in extensive electron exchange between heme sites of the hybridizing sample, leading to incorrect evaluation of the equilibrium species population by the cryogenic techniques that have been employed. In this report, we demonstrate that neither appreciable cyanide loss nor electron exchange occurs with the methods that have been used extensively by our two labs. for these equilibrium detns. [Perrella et al. (1990) Biophys. Chemical 35, 97-103; Daugherty et al. (1991) Proc. Natl. Acad. Sci. U.S.A. 88, 1110-1114]. An alternative experiment, which Shibayama et al. (1997) have carried out to illustrate their claim, does not evaluate a **thermodn.** equilibrium property of the species [21] hybrid. The relevance of their newly-estimated "free energy" is therefore unclear. Nevertheless, Shibayama et al. (1997) have claimed that their proposed "free energy" (which is .apprx.1.3 kcal more pos. than the free energy of -11.4 kcal found independently by our two labs.) renders invalid the mol. code mechanism of Hb cooperativity. This representation is utterly without foundation since a free energy even more pos. than suggested by Shibayama et al. (1997) would be fully consistent with the mol. code mechanism.

CC 6-1 (General Biochemistry)

ST Hb cooperativity **tetramer** conformation free energy; cyanometHb cooperativity **tetramer** conformation free energy; cyanide release electron exchange Hb cooperativity

IT **Hemoglobins, methemoglobins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyanometHbs; **thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(α.beta.) and methodol. and mechanistic issues)

IT Electron transfer
(intramol., between heme sites; **thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(αβ) and methodol. and mechanistic issues)

IT Quaternary structure
(protein, transition; **thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(α.beta.) and methodol. and mechanistic issues)

IT Conformational free energy
Cooperative phenomena
(**thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(αβ) and methodol. and mechanistic issues)

IT **Hemoglobins**
Hemoglobins, methemoglobins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(αβ) and methodol. and mechanistic issues)

IT 57-12-5, Cyanide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(release from cyanometHb; **thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(αβ) and methodol. and mechanistic issues)

IT **9034-51-9**, Hemoglobin A
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**thermodn. stability** of asym. doubly-ligated Hb **tetramer** (α+CNβ+CN)(αβ) and methodol. and mechanistic issues)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 21 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:738716 HCAPLUS
DOCUMENT NUMBER: 128:16357
TITLE: A discussion of limitations on the use of **polymers** for **stabilization** of proteins during the freezing portion of lyophilization
AUTHOR(S): Barbieri, David M.; Heller, Martin C.; Randolph, Theodore W.; Carpenter, John F.
CORPORATE SOURCE: Department of Chemical Engineering, ECCH 111, University of Colorado, Boulder, CO, 80309-0424, USA
SOURCE: ACS Symposium Series (**1997**), 675(Therapeutic Protein and Peptide Formulation and Delivery), 90-108
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Nov 1997
AB A **thermodn.** model based on the theor. framework of Timasheff and coworkers has been developed to consider the protein stabilization offered by polymeric co-solvents. Inspection of such systems reveals that the large transfer free energies (and presumably protein stability) rendered by polymeric excipients such as poly(ethylene glycol) increase with increasing polymer concentration These same polymers, however, commonly induce phase splits in aqueous solns., presenting limitations to the protection conferred. Further consideration of freeze-drying formulations suggest that such phase splits are a likely consequence of the concentrating effects of freezing aqueous solns. Exptl. studies of Hb lyophilized in polyethylene glycol/dextran mixts. give evidence that liquid /liquid phase separation per se occurring during the course of the lyophilization cycle can have detrimental effects on the structural integrity of protein in the dried state.
CC 63-5 (Pharmaceuticals)
ST lyophilization **polymer stabilization** freezing; protein **stabilization** lyophilization **polymer**
IT Freeze drying
(**polymers** for **stabilization** of proteins during freezing portion of lyophilization)
IT **Hemoglobins**
Polymers, biological studies
Polyoxyalkylenes, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**polymers** for **stabilization** of proteins during freezing portion of lyophilization)
IT 9004-54-0, Dextran, biological studies 25322-68-3, Polyethylene glycol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**polymers** for **stabilization** of proteins during freezing portion of lyophilization)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L122 ANSWER 22 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:748377 HCAPLUS
DOCUMENT NUMBER: 126:22869
TITLE: Hemoglobin chromatographic purification from erythrocyte and preparation of **stable** **polymerized** hemoglobin blood-substitute
INVENTOR(S): Rausch, Carl W.; Gawryl, Maria S.; Houtchens, Robert A.; Laccetti, Anthony J.; Light, William R.; Jacobs, Edward E., Jr.
PATENT ASSIGNEE(S): Biopure Corporation, USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9629346	A1	19960926	WO 1996-US4030	19960322 <--
W: AU, CA, JP, NZ				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5854209	A	19981229	US 1995-409337	19950323 <--
US 5840852	A	19981124	US 1995-458916	19950602 <--
US 5691452	A	19971125	US 1995-471583	19950607 <--
US 5753616	A	19980519	US 1995-478004	19950607 <--
US 5955581	A	19990921	US 1995-484775	19950607 <--
AU 9653227	A1	19961008	AU 1996-53227	19960322 <--
AU 705225	B2	19990520		
EP 815138	A1	19980107	EP 1996-909855	19960322 <--
EP 815138	B1	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11502821	T2	19990309	JP 1996-528657	19960322 <--
NZ 305258	A	20001027	NZ 1996-305258	19960322 <--
AT 222926	E	20020915	AT 1996-909855	19960322 <--

PRIORITY APPLN. INFO.:

US 1995-409337	A	19950323 <--
US 1995-458916	A	19950602 <--
US 1995-471583	A	19950607 <--
US 1995-473497	A	19950607 <--
US 1995-478004	A	19950607 <--
US 1995-484775	A	19950607 <--
US 1986-928345	B2	19861110 <--
US 1987-107421	B2	19871013 <--
US 1987-119121	A1	19871110 <--
US 1992-820153	A1	19920113 <--
US 1994-209949	A2	19940311 <--
US 1995-487288	A	19950607 <--
WO 1996-US4030	W	19960322 <--

ED Entered STN: 21 Dec 1996
AB A method for producing a stable polymerized Hb blood-substitute from blood characterized in the use of a chromatog. column, is disclosed. The method of this invention includes mixing blood with an anticoagulant to form a blood solution, washing the red blood cells in the blood solution and then separating

the washed red blood cells from the white blood cells. This method also includes disrupting the red blood cells to release Hb and form a Hb solution, which is then treated by high performance liquid chromatog. to form a Hb eluate. The Hb eluate is then deoxygenated, contacted with a first reducing agent to form an oxidation-stabilized deoxygenated Hb solution, and mixed with a crosslinking agent to form a polymerization reaction mixture which is then polymerized The polymerized Hb solution is then diafiltered with a physiol. solution and with a reducing agent, whereby the polymerized Hb solution is made physiol. acceptable, and whereby the reducing agent scavenges oxygen, to form a stable polymerized Hb blood-substitute, which is then packaged and stored in an atmospheric substantially free of oxygen. Compns. made by the methods are also disclosed, as are methods of therapeutically, or prophylactically, treating a vertebrate to increase tissue oxygenation, or prevent oxygen depletion, in tissue of the vertebrate.

IC ICM C07K014-805
ICS C07K001-18; A61K038-42

CC 63-3 (Pharmaceuticals)

ST blood substitute **polymd stable** Hb

IT Blood substitutes
HPLC
(Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT **Hemoglobins, methemoglobins**
Hemoglobins, oxyhemoglobins
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT **Hemoglobins**
RL: PUR (Purification or recovery); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Ion exchange chromatography
(affinity; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Anticoagulants
(blood solution preparation; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Blood preservation
(blood substitute storage in oxygen-free atmospheric; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Erythrocyte
(chromatog. for Hb purification; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Dialdehydes
RL: RCT (Reactant); RACT (Reactant or reagent)
(crosslinking agent; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Ultrafiltration
(diafiltration; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

IT Toxins
RL: REM (Removal or disposal); PROC (Process)
(endotoxins, ion-exchange affinity separation of Hb and endotoxin; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT Reducing agents
(oxidation-**stabilized**, deoxygenated Hb solution preparation; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT Crosslinking agents
(**polymerized** Hb preparation; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT **Heat**
(**polymerization**; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT **Hemoglobins**
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products, **polymerized**, preparation and purification; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT 111-30-8, Glutaraldehyde
RL: CAT (Catalyst use); USES (Uses)
(crosslinking agent; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)
IT 616-91-1, N-Acetyl-cysteine 16940-66-2, Sodium borohydride
RL: CAT (Catalyst use); USES (Uses)
(reducing agent; Hb chromatog. purification from erythrocyte and preparation of **stable polymerized** Hb blood-substitute)

L122 ANSWER 23 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:116450 HCAPLUS
DOCUMENT NUMBER: 126:162321
TITLE: Hemoglobin liposomes stable in blood
INVENTOR(S): Endo, Saori; Awai, Koji; Yano, Yoshihiro; Nakano, Yoshiro; Mori, Masato
PATENT ASSIGNEE(S): Nippon Oils & Fats Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08333241	A2	19961217	JP 1995-144361	19950612 <--
JP 3572428	B2	20041006		
PRIORITY APPLN. INFO.:			JP 1995-144361	19950612 <--

ED Entered STN: 20 Feb 1997
AB Hb liposomes stable in blood are prepared by encapsulation of Hbs, suspension of the liposomes in an aqueous phase containing 0.05-50 g/dL radical-scavenging water soluble compds. such as EDTA and Hbs, and irradiation to form polymerized Hb liposomes stable in blood. The method can be applied to preparing drug delivery systems.
IC ICM A61K009-127

ICS A61K009-127; B01J013-04; A61K038-16
CC 63-7 (Pharmaceuticals)
IT **Hemoglobins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of irradiation-**polymerized** Hb liposomes **stable** in blood)

L122 ANSWER 24 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:77830 HCAPLUS
DOCUMENT NUMBER: 124:197669
TITLE: **Stabilization** of the **tetrameric** structure of human and bovine hemoglobins by pseudo-crosslinking with muconic acid
AUTHOR(S): Razynska, Anna; Matheson-Urbaitis, Barbara; Fronticelli, Clara; Collins, John H.; Bucci, Enrico
CORPORATE SOURCE: Dept. Biochem., School Medicine, University Maryland, Baltimore, MD, 21201, USA
SOURCE: Archives of Biochemistry and Biophysics (**1996**), 326(1), 119-25
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Feb 1996
AB In previous studies mono(3,5-dibromosalicyl)fumarate was used to introduce an intramol. crosslink (pseudo-crosslink) in the β cleft between Hb β subunits. Sedimentation velocity anal. indicated that the product had a mean mol. weight indicating a tetramer with low dissociability. The product had a P50 higher than that of native Hb and a plasma retention **time** in rat of about 3 h, i.e., 4 **times** longer than untreated Hb. However, the product contained a fraction which was rapidly eliminated in the urine and which had a short plasma half-**time** of about 20 min, indicating the presence of a dissociable fraction. The authors attempted to further enhance the tetrameric stability of Hb and prevent urine elimination by positioning a longer chain carboxylic acid than fumaric acid into the β cleft. They reason that a longer mol. would allow for greater stabilizing interactions across the β cleft. In the present study, human and bovine Hbs were reacted with mono(3,5-dibromosalicyl)muconate. Muconic acid is 2 carbons longer than fumaric acid. The products were acylated at the β82 (human) and β81 (bovine) lysines of the β-cleft and had a low degree of dissociability. For reasons not presently understood, urine excretion was high and plasma half-**time** was not increased above that of untreated Hb. Apparently, only covalently crosslinked Hbs which are completely nondissociable tetramers escape filtration; tetramers with any degree of dissociability into dimers are filterable.
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 63
ST Hb **tetramer stabilization** pseudo crosslinking muconate; bromosalicylmuconate pseudo crosslinking Hb **tetramer**
IT Blood substitutes and Plasma expanders
Bohr effect
Crosslinking
(**stabilization** of **tetrameric** Hbs by pseudo-crosslinking with muconic acid)
IT **Hemoglobins**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**stabilization** of **tetrameric** Hbs by

pseudo-crosslinking with muconic acid)
IT 7782-44-7, Oxygen, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**stabilization** of **tetrameric** Hbs by pseudo-crosslinking with muconic acid)
IT **9034-51-9**, HbA 10519-96-7, Potassium trimethylsilanolate 174416-74-1 174416-76-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(**stabilization** of **tetrameric** Hbs by pseudo-crosslinking with muconic acid)
IT 174416-75-2P 174416-77-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**stabilization** of **tetrameric** Hbs by pseudo-crosslinking with muconic acid)

L122 ANSWER 25 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:563794 HCAPLUS
DOCUMENT NUMBER: 121:163794
TITLE: Quantitative transformation of hemoglobin into stable tetramers
AUTHOR(S): Benesch, R. E.; Kwong, S.
CORPORATE SOURCE: Coll. Phys. Surg., Columbia Univ., New York, NY, 10032, USA
SOURCE: Hemoglobin (**1994**), 18(3), 185-92
CODEN: HEMOD8; ISSN: 0363-0269
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Oct 1994
AB A method is described for the preparation of human or bovine Hb with a covalent bridge, formed by bispyridoxal-tetraphosphate, between the β chains. The yield is 95% of the total Hb. The location of the two mols. of bispyridoxal-tetraphosphate in the tetramer has been established. The functional properties of the cross-linked Hb, its stability, and particularly, the simplicity of the method for its preparation, make it a promising candidate for an acellular blood substitute.
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 9, 13
IT **Hemoglobins**
RL: PROC (Process)
(transformation of, in **stable tetramers**, bispyridoxal tetraphosphate in)

L122 ANSWER 26 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:367387 HCAPLUS
DOCUMENT NUMBER: 123:42984
TITLE: Study on the electron-transfer process between electrode and proteins in **polymer** solvents
AUTHOR(S): Ohno, Hiroyuki
CORPORATE SOURCE: Dep. Biotechnol., Tokyo Univ. Agric. Technol., Koganei, 184, Japan
SOURCE: Asahi Garasu Zaidan Josei Kenkyu Seika Hokoku (**1994**) 183-9
CODEN: AGSHEN; ISSN: 0919-9179
PUBLISHER: Asahi Garasu Zaidan
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
ED Entered STN: 22 Feb 1995
AB The electron transfer process between electrode and heme-containing proteins

was analyzed in poly(ethylene oxide), a typical ion conductive polymer. PEO-modified heme-proteins (Hb and myoglobin) were cast onto the ITO electrode, and soaked into a salt-containing PEO oligomer. These proteins showed quasi-reversible electron transfer in the PEO by the change in potential. Proteins on the ITO electrode showed fast electron transfer, but successive electron transfer between adjacent proteins in the layer was revealed to be slow. Excellent **thermal** stability of the PEO-modified proteins in PEO was confirmed, and quasi-reversible electron transfer was observed even above 100°C.

CC 72-2 (Electrochemistry)
Section cross-reference(s): 6

IT Electrodes
(ITO; electron-transfer process between electrodes and heme-containing proteins in **polymer** solvents)

IT Electron exchange and Charge transfer
(electron-transfer process between electrodes and heme-containing proteins in **polymer** solvents)

IT **Hemoglobins**
Hemoproteins
Myoglobins
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(poly(ethylene oxide)-modified, electron transfer with electrode and **thermal stability** of; electron-transfer process between electrodes and heme-containing proteins in **polymer** solvents)

IT 25322-68-3D, complex with heme-containing proteins
RL: MOA (Modifier or additive use); USES (Uses)
(electron transfer occurring in; electron-transfer process between electrodes and heme-containing proteins in **polymer** solvents)

L122 ANSWER 27 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:551574 HCAPLUS
DOCUMENT NUMBER: 121:151574
TITLE: The dimer-tetramer equilibrium of recombinant hemoglobins. Stabilization of the α1β2 interface by the mutation β(Cys112→Gly) at the α1β1 interface
AUTHOR(S): Fronticelli, Clara; Gattoni, Maurizio; Lu, A-Lien; Brinigar, William S.; Bucci, Jeffries L. G.; Chiancone, Emilia
CORPORATE SOURCE: Department of Biochemistry, University of Maryland, School of Medicine, 108 N. Greene St., Baltimore, MD, USA
SOURCE: Biophysical Chemistry (**1994**), 51(1), 53-7
CODEN: BICIAZ; ISSN: 0301-4622
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Oct 1994
AB The dimer-tetramer association consts. of several recombinant human Hbs (in the CO form) have been measured by differential gel filtration. Recombinant human Hb prepared from recombinant β-chains, and mutant Hbs where the substitution was on the surface, β(Thr4→Asp), in the heme pocket, β(Val67→Thr), at the 2,3-DPG binding site, β(Val1→Met+His2del), had a twofold smaller association with respect to natural Hb. In a mutant at the α1β2 interface, β(Cys93→Ala), the association constant was decreased three-fold. Conversely, in a mutant at the α1β1 interface, β(Cys112→Gly), the association constant was two- and four-fold increased with respect to natural and recombinant human Hb. These differences are energetically very small, consistent with the correct

folding of the recombinant Hbs. The stabilization of the tetrameric structure by a mutation at the α1β1 interface indicates that structural changes at this interface can be propagated through the protein to the α1β2 interface and, thereby, exert an effect on the allosteric equilibrium

CC 6-3 (General Biochemistry)

IT **Hemoglobins**
RL: PRP (Properties)
(dimer-**tetramer** equilibrium in, subunit interface **stabilization** in relation to)

L122 ANSWER 28 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:485533 HCAPLUS
DOCUMENT NUMBER: 119:85533
TITLE: Phosphorothioate-phosphodiester oligonucleotide co-**polymers**: Assessment for antisense application
AUTHOR(S): Ghosh, Mridul K.; Ghosh, Krishnakali; Cohen, Jack S.
CORPORATE SOURCE: Med. Cent., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Anti-Cancer Drug Design (**1993**), 8(1), 15-32
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Sep 1993
AB Efforts have been made to reduce the disadvantages associated with the natural oligonucleotides (all-PO) for antisense application by introducing phosphorothioate (PS) linkages into the mol. A series of such oligodeoxynucleotide copolymers (17-mers) complementary to the coding region of the rabbit β-globin mRNA, and containing different proportions and arrangements of PO and PS bonds, were synthesized and tested for their protein-binding properties, nuclease stability in vitro, hybridizing ability with cDNA, ability to form RNase H-sensitive substrates and antisense activity in cell-free systems. The melting **temps.** (Tm) of the co-polymers were reduced by up to 6° relative to the all-hybridizing abilities of the co-polymers. The protein-binding studies with human serum albumin exhibited a linear correlation with the percentage of PS linkage present in the mol. Nuclease susceptibilities of the co-polymers were also improved, but the number and position of the PS linkages played a significant role in such improvement. Translation inhibition by these oligonucleotides was only found in wheat germ agglutinin (WGA) extract, but not in rabbit reticulocyte lysate (RRL) cell-free system, suggesting the involvement of RNase H in their antisense activities. Provided they have ≥50% PS linkages, the co-polymers produced almost the same increased inhibition in the WGA system as that of the all-PS oligo. The translation arrest in WGA extract is in good agreement with the in vitro cleavage found for rabbit globin mRNA in the oligo:mRNA duplex by RNase H alone. It is concluded that a copolymer of PO and PS might be preferable to either all-PO or all-PS for antisense applications.

CC 1-6 (Pharmacology)

IT **Hemoglobins**
RL: BIOL (Biological study)
(β-chain, mRNA of, antisense phosphorothioate-phosphodiester nucleotide **copolymers** for, translation inhibition by and nuclease **stability** of)

IT Nucleotides, **polymers**
RL: BIOL (Biological study)
(oligo-, phosphorothioate-phosphodiester copolymers as, translation inhibition by and nuclease **stability** of)

IT 9050-76-4, RNase H
RL: BIOL (Biological study)

(antisense phosphorothioate-phosphodiester nucleotide copolymers **stability** to)
IT 110278-62-1 149225-17-2 149225-18-3 149225-19-4 149225-20-7
149225-21-8 149225-22-9 149225-23-0 149225-24-1
RL: BIOL (Biological study)
(translation inhibition by and nuclease **stability** of, as antisense oligonucleotide, phosphorothioate and phosphodiester linkages in relation to)

L122 ANSWER 29 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:260774 HCAPLUS
DOCUMENT NUMBER: 118:260774
TITLE: Stability and blood compatibility of polylipid/Hb
AUTHOR(S): Morizawa, K.; Akama, K.; Kawakami, Y.; Tsuchida, E.
CORPORATE SOURCE: Tsukuba Res. Lab., Nippon Oil and Fats Co., Tsukuba, 300-26, Japan
SOURCE: Biomaterials, Artificial Cells, and Immobilization Biotechnology (**1992**), 20(2-4), 641-5
CODEN: BACBEU; ISSN: 1055-7172
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Jun 1993
AB The Polylipid/Hb vesicle is a new artificial red cell (ARC) based on liposome-encapsulated Hb. Advantages are derived from the stabilized liposomal bilayer membranes, obtained by polymerization of 1,2-bis(2,4-octadecadienoyl)-sn-glycero-3-phosphocholine (DODPC). Furthermore, blood compatibility in vitro are good.
CC 63-3 (Pharmaceuticals)
IT **Hemoglobins**
RL: BIOL (Biological study)
(liposomes containing bis(octadecadienoyl)glycerophosphocholine for encapsulation of, **polymerizable**, blood compatibility and **stability** of, as artificial erythrocyte)

L122 ANSWER 30 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:225238 HCAPLUS
DOCUMENT NUMBER: 118:225238
TITLE: Hemoglobin tetramers stabilized with polyaspirins
AUTHOR(S): Bucci, Enrico; Fronticelli, Clara; Razynska, Anna; Militello, Valeria; Koehler, Raymond; Urbaitis, Barbara
CORPORATE SOURCE: Med. Sch., Univ. Maryland, Baltimore, MD, 21201, USA
SOURCE: Biomaterials, Artificial Cells, and Immobilization Biotechnology (**1992**), 20(2-4), 243-52
CODEN: BACBEU; ISSN: 1055-7172
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 Jun 1993
AB Organic acids activated by esterification with 3,5-dibromosalicylate react preferentially either with the β82 lysines or the α99 lysines of Hb. The versatility and site specificity of these polyaspirins and the usage of both human and bovine Hbs allowed the construction of a family of oxygen carriers with various P50 ranging from 10 to 50 mmHg. These derivs. are obtained in pure homogeneous form by column chromatog. They are stabilized tetramers where the dissociation into dimers is inhibited. The latest addition is Tris(3,5-dibromosalicyl)benzenetricarboxylate, which crosslinks both human and bovine Hb across the β subunits, decreasing the oxygen affinity of both proteins. The crosslinked Hbs have a normal Bohr effect, more expanded in the alkaline region, and are sensitive to chlorides but not to polyphosphates. Solns. of stabilized tetramers,

infused into rats or cats up to 25-50% blood replacement, do not produce altered renal and cardiac function. In the cat, isovolemic hemodilution increases cerebral flow in controls treated with albumin solns.; when an oxygen carrier is used, the cerebral flow remains normal.

CC 1-8 (Pharmacology)

IT **Hemoglobins**
RL: BIOL (Biological study)
(**tetramers, stabilization** of, with polyaspirins)

L122 ANSWER 31 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:637819 HCAPLUS
DOCUMENT NUMBER: 113:237819
TITLE: Hemoglobin-based blood substitute
INVENTOR(S): Ilan, Ehud; Lotan, Noah; Cohen, Tova; Sideman, Samuel
PATENT ASSIGNEE(S): Technion Research and Development Foundation Ltd., Israel
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 361720	A1	19900404	EP 1989-309170		19890908	<--
R: AT, DE, ES, FR, GB, IT, SE						
IL 87708	A1	19940412	IL 1988-87708		19880908	<--
PRIORITY APPLN. INFO.:			IL 1988-87708	A	19880908	<--

ED Entered STN: 22 Dec 1990

AB Hb-based blood substitute is prepared from stroma-free Hb, intramol.-stabilized, modified with pyridoxal-5'-phosphate and subsequently ≥40% polymerized under anaerobic conditions. The blood substitute is not toxic and possesses the proper O affinity, adequate oncotic pressure and percentage of metHb equal to that of whole human blood. It has appropriate lifetime in circulation upon reconstitution, good O binding and delivery characteristics and appropriate O transport capacity. Crystals of stroma-free Hb were dialyzed against water and Tris-HCl buffer (pH 7.4), sterilized with antibiotics and treated with bis(3,5-dibromosalicyl)fumarate (pH 8). The intramol.-stabilized Hb obtained was pyridoxylated with pyridoxal-5'-phosphate, followed by reduction with NaBH4, polymerization using glutaraldehyde as crosslinking reagent, and quenching with ethanolamine.

IC ICM A61K037-14

CC 63-3 (Pharmaceuticals)

IT **Hemoglobins**
RL: PREP (Preparation)
(stroma-free, **stabilization** and pyridoxylation and **polymerization** of, in blood substitute preparation)

L122 ANSWER 32 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1988:156311 HCAPLUS
DOCUMENT NUMBER: 108:156311
TITLE: Stability of hemoglobin polymers
AUTHOR(S): Vyazova, E. P.; Fetisova, L. V.; Azhigirova, M. A.; Khachatur'yan, A. A.
CORPORATE SOURCE: TsNII Gematol. Pereliv. Krovi, Moscow, USSR
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (**1988**), 22(1), 81-4
CODEN: KHFZAN; ISSN: 0023-1134

DOCUMENT TYPE: Journal
LANGUAGE: Russian
ED Entered STN: 30 Apr 1988
AB Among various sugars used as cryoprotectants for pyridoxalated Hb polymers (HPH), glucose and sorbitol showed the best properties. Freeze-dried HPH stored at -20° and protected with either of these 2 compds. was stable for ≥1 yr. When sorbitol (0.5 g/1 g PHP) was used, no oxidation was observed, while in the presence of glucose, minor oxidation (<1%/1 yr) was observed
CC 63-3 (Pharmaceuticals)
IT **Hemoglobins**
RL: BIOL (Biological study)
(reaction products, with pyridoxal phosphate, **polymerized**, **stability** of freeze-dried)

L122 ANSWER 33 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:2333 HCAPLUS
DOCUMENT NUMBER: 108:2333
TITLE: Effect of amino acid at the β6 position on surface hydrophobicity, stability, solubility, and the kinetics of polymerization of hemoglobin. Comparisons among Hb A (Gluβ6), Hb C (Lysβ6), Hb Machida (Glnβ6), and Hb S (Valβ6)
AUTHOR(S): Adachi, Kazuhiko; Kim, Jungyop; Travitz, Ron; Harano, Teruo; Asakura, Toshio
CORPORATE SOURCE: Div. Hematol., Child. Hosp. Philadelphia, Philadelphia, PA, 19104, USA
SOURCE: Journal of Biological Chemistry (**1987**), 262(27), 12920-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Jan 1988
AB Surface hydrophobicity, stability, solubility, and kinetics of polymerization were studied in Hbs containing 1 of 4 different amino acids at the β6 position: Hb A (Gluβ6), Hb C (Lysβ6), Hb Machida (Glnβ6), and Hb S (Valβ6), (where Glu is glutamate, Lys is lysine, Gln is glutamine, and Val is valine). The surface hydrophobicity increased in the order of Hb C < Hb A < Hb Machida < Hb S, coinciding with the hydrophobicity of the amino acid at the β6 position. Solubility of the oxy form of these Hbs decreased in relation to increases in their surface hydrophobicity, suggesting that the solubility is controlled by the strength of hydrophobicity of the amino acid at the β6 position. The solubility of the oxy form of these Hbs is always higher than that of the deoxy form. There is a similar linear relationship between the solubility and surface hydrophobicity among deoxyHbs A, C, and Machida. However, the solubility of deoxyHb S deviated significantly from the expected value, indicating that the extremely low solubility of deoxyHb S is not directly related to the hydrophobicity of the β6 valine. Kinetic studies on the polymerization of deoxyHb Machida revealed a distinct delay prior to polymerization, confirming the previous hypothesis that β6 valine is not responsible for the delay prior to gelation. The kinetics of the polymerization of 1:1 mixts. of sickle and non-sickle Hbs were similar to those of pure Hb S, suggesting that only 1 of the 2 β6 valines is involved in an intermol. contact. In mixts. of equal amts. of Hb S and Hb A, Hb C, or Hb Machida, half of the asym. AS, SC, and S-Machida hybrid Hbs behaved like Hb S during nucleation, whereas the other half behaved like the non-sickle Hb.

CC 6-3 (General Biochemistry)
Section cross-reference(s): 14
IT **Hemoglobins**
RL: BIOL (Biological study)
(surface hydrophobicity and **stability** and solubility of, kinetics of **polymerization** in relation to)
IT **9034-51-9**, Hemoglobin A
RL: BIOL (Biological study)
(surface hydrophobicity and **stability** and solubility of, amino acids substitution at β6 position effects on, kinetics of **polymerization** in relation to)
IT 9008-00-8, Hemoglobin C **9035-22-7**, Hemoglobin S 84419-50-1, Hemoglobin Machida
RL: BIOL (Biological study)
(surface hydrophobicity and **stability** and solubility of, β6 position function in, kinetics of **polymerization** in relation to)

L122 ANSWER 34 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:90029 HCAPLUS
DOCUMENT NUMBER: 106:90029
TITLE: Study of prolonged storage of hemoglobin polymer solutions
AUTHOR(S): Vyazova, E. P.; Fetisova, L. V.; Azhigirova, M. A.; Shuvalova, A. L.; Khachaturyan, A. A.
CORPORATE SOURCE: TsNII Gematol. Pereliv. Krovi, Moscow, USSR
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (**1986**), 20(11), 1360-3
CODEN: KHFZAN; ISSN: 0023-1134
DOCUMENT TYPE: Journal
LANGUAGE: Russian
ED Entered STN: 21 Mar 1987
AB Pyridoxalated and polymerized Hbs (pH 7.4) blood substitutes, were stable for several mo. at 4-6° by addition of stabilizing agents. among 6 stabilizers studied, the most effective were NAD [53-84-9] and NAD phosphate [53-59-8], showing reducing effect, and sorbitol [50-70-4], preventing the oxidation Hbs can be stored for several mo by addition of sorbitol, and 1/2 yr and longer by addition of NAD and NAD phosphate in 10-fold greater concentration than met-Hb content.
CC 63-3 (Pharmaceuticals)
IT **Hemoglobins**
RL: BIOL (Biological study)
(reaction products, with pyridoxal phosphate, **polymerized**, **stabilizing** agents for, for blood substitutes)

L122 ANSWER 35 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:213174 HCAPLUS
DOCUMENT NUMBER: 104:213174
TITLE: Study of the functional activity of the hemoglobin polymer, a lyophilized oxygen carrier
AUTHOR(S): Fetisova, L. V.; Vyazova, E. P.; Azhigirova, M. A.; Khachaturyan, A. A.
CORPORATE SOURCE: Tsentr. NII Gematol. Perelivan. Krovi, Moscow, USSR
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (**1986**), 20(2), 214-17
CODEN: KHFZAN; ISSN: 0023-1134
DOCUMENT TYPE: Journal
LANGUAGE: Russian
ED Entered STN: 14 Jun 1986
AB The effect of lyophilization on the activity of polyHb, modified by pyridoxal 5'-phosphate (PHPP) was studied. During lyophilization 40-50%

PHPP was transformed to inactive met-Hb. Addition of sucrose [57-50-1], glucose [50-99-7], phycol [62611-31-8], Tris [77-86-1] or polyethylene glycol 4000 [25322-68-3] stabilized the PHPP. In the presence of stabilizers, PHPP retained its effectiveness for oxygen transport during lyophilization and the met-Hb content was almost the same as in natural Hb. Thus, stabilizers should be used during storage of lyophilized PHPP product.

CC 63-7 (Pharmaceuticals)

IT **Hemoglobins**
RL: BIOL (Biological study)
(**polymers**, pyridoxylated, as oxygen carriers, **stabilization** of, during lyophilization)

L122 ANSWER 36 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:519239 HCAPLUS
DOCUMENT NUMBER: 103:119239
TITLE: Intrinsic fluorometric determination of the stable state of aggregation in hemoglobins
AUTHOR(S): Hirsch, Rhoda Elison; San George, Richard C.; Nagel, Ronald L.
CORPORATE SOURCE: Dep. Med., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SOURCE: Analytical Biochemistry (**1985**), 149(2), 415-20
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 Oct 1985
AB Stable aggregation states of Hbs from clams (dimeric and tetrameric Hbs) and humans (tetrameric Hb A) were determined by measuring their intrinsic fluorescence by fluorometry with front-face optics. Clam (Noetia ponderosa and Anadara ovalis) Hb components exhibited fluorescence properties different from those of Hb A. The stable dimeric Hb components exhibited fluorescence emission maximum shifted to longer wavelengths compared to tetrameric human Hb. Conversely, the tetrameric major Hb component of A. ovalis exhibited an emission maximum similar to that of tetrameric Hb A. Hence, stable dimeric Hbs can be detected by emission maximum at longer wavelengths relative to Hb A. Fluorescence studies of ligand binding to these clam Hbs indicate structural and functional differences among these components and compared to Hb A. Thus, different stable aggregation states of Hbs may be determined by intrinsic fluorescence when studied with front-face optics. The method is simple, inexpensive, eliminates inner-filter effects, and can be applied to other heme proteins, macromols., and cell organelles with high extinction coeffs. of absorption and/or light scatter.
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 12
IT **Hemoglobins**
RL: PRP (Properties)
(**stable** aggregation states of, determination of, of clams and humans by front-face fluorometry)
IT **9034-51-9**
RL: ANST (Analytical study)
(**tetramer**, determination of, of humans by front-face fluorometry)

L122 ANSWER 37 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1984:606346 HCAPLUS
DOCUMENT NUMBER: 101:206346
TITLE: Relationship between tetramer-dimer assembly and the stability of Hb Malmoe ($\alpha 2\beta 297$Gln)

AUTHOR(S): Adachi, K.; Vonk, H.; Reilly, M. P.; Adachi, H.; Schroeder, W. A.; Schwartz, E.; Asakura, T.
CORPORATE SOURCE: Div. Hematol., Child. Hosp. Philadelphia, Philadelphia, PA, 19104, USA
SOURCE: Biochimica et Biophysica Acta, Protein Structure and Molecular Enzymology (**1984**), 790(2), 132-40
CODEN: BBAEDZ; ISSN: 0167-4838
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 Sep 2005
AB The effects of mutation at the α1β2 contact in Hb Malmoe (α2β297(FG4)His→Gln) on O-binding properties, ease of dissociation into dimeric Hb, and stability were studied. The P50 value of Hb Malmoe in the absence of organic phosphates was 1.9 mm Hg, in contrast to 8.8 mm Hg for Hb A. The n value determined from a Hill plot of Hb Malmoe was 1.6. The overall free energy of interaction of O with Hb Malmoe was .apprx.25% that of Hb A. The Adair constant, K1, of Hb Malmoe was .apprx.10-fold larger than that of Hb A, but the K4 of Hb Malmoe was similar to that of Hb A. The liganded form of Hb Malmoe dissociated into dimers more readily than Hb A on gel filtration on Sephadex G-100. Dissociation into dimeric Hb was enhanced in dilute solns. Increased instability during mech. agitation of diluted samples was greater for Hb Malmoe than for Hb A. The denaturation rate consts. of tetramers of the oxyHb A and oxyHb Malmoe were .apprx.20-fold greater than those of dimers of these Hbs. The instability of Hb Malmoe depends on a greater α1β2 dissociation constant compared with that of Hb A. The role of the intersubunit contact in determining the functional properties and the stability of the Hb mol. are discussed.
CC 6-3 (General Biochemistry)
IT **9034-51-9**
RL: BIOL (Biological study)
(oxygen binding and dimer-**tetramer** assembly and **stability** of, of human, Hb Malmoe comparison with)

L122 ANSWER 38 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1984:98530 HCAPLUS
DOCUMENT NUMBER: 100:98530
TITLE: Effect of malondialdehyde, a product of lipid peroxidation, on the function and stability of hemoglobin
AUTHOR(S): Kikugawa, Kiyomi; Kosugi, Hiroko; Asakura, Toshio
CORPORATE SOURCE: Child. Hosp. Philadelphia, Univ. Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Archives of Biochemistry and Biophysics (**1984**), 229(1), 7-14
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB Malondialdehyde (MDS) reacted with normal Hb A to form a number of less cationic components which were detected by cellulose acetate electrophoresis and gel electrofocusing. All the modified components moved down the cation-exchange resin more quickly than did Hb A, a chromatog. behavior similar to that of glycosylated Hb A. Some of the modified components were intermol. crosslinked, and showed fluorescence with an excitation maximum at 390 nm and an emission maximum at 460 nm. MDA probably reacts nonspecifically with the ε-amino groups of lysine and N-terminal amino groups to produce aminoacrolein, crosslinks, and strongly fluorescent 1,4-dihydropyridine-3,5-dicarbaldehyde. O affinity of the modified Hbs was increased. The modified Hbs were more readily

oxidized into the met-form. Mech. stability of Hb A was also decreased by modification. A considerable conformational change in Hb A was apparently induced by the treatment with MDA. Since MDA is generated in erythrocytes as a consequence of lipid peroxidn., MDA may react with intracellular Hb A and influence the function and the stability of Hb.

CC 6-3 (General Biochemistry)

IT **9034-51-9D**, reaction products with malondialdehyde
RL: BIOL (Biological study)
(function and **stability** of, of human)

IT **9035-22-7D**, reaction product with malondialdehyde
RL: BIOL (Biological study)
(**polymerization** and solubility of, of human)

L122 ANSWER 39 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:498825 HCAPLUS
DOCUMENT NUMBER: 99:98825
TITLE: Sickle cell disease: the proportion of liganded hemoglobin needed to prevent crises
AUTHOR(S): Franklin, I. M.; Rosemeyer, M. A.; Huehns, E. R.
CORPORATE SOURCE: Dep. Haematol., Univ. Coll. London, London, WC1, UK
SOURCE: British Journal of Haematology (**1983**), 54(4), 579-87
CODEN: BJHEAL; ISSN: 0007-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB In an attempt to predict the likelihood of successfully treating sickle cell disease by increasing Hb S (HbS) [**9035-22-7**] O affinity, 2 liganded derivs. of Hb S were studied in an in vitro system that measures deoxy-Hb S **polymerization** The participation of these liganded forms in the **polymers** was quantitated in terms of an exclusion factor that relates their behavior to that of deoxy-Hb S. Carbonmonoxy-Hb S had an oxy-Hb-like conformation and did not participate significantly in the **polymerization** It was calculated that 30% carbonmonoxy-Hb S would have to be maintained in vivo to prevent sickling. Met-Hb S had a conformational equilibrium intermediate between oxy- (or carbonmonoxy-) and deoxy-Hb S and behaved in a similarly intermediate manner with regard to deoxy-Hb S **polymerization** 60% Met-Hb S would be needed to prevent in vivo sickling. Thus, **stabilizing** the oxy(R)-conformation is a potentially useful way of preventing sickling, and a level of 30% R-state Hb S would have to be maintained for this to be successful.

CC 1-3 (Pharmacology)

IT **9035-22-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**polymerization** of, conversion to carbonmonoxy-Hb S or met-Hb S effect on, in humans)

L122 ANSWER 40 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1974:473677 HCAPLUS
DOCUMENT NUMBER: 81:73677
TITLE: Interaction of human hemoglobin with heptoglobin or antihemoglobin antibody
AUTHOR(S): Sasazuki, Takehiko; Tsunoo, Hajime; Nakajima, Hiroshi; Imai, Kiyohiro
CORPORATE SOURCE: Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo, Japan
SOURCE: Journal of Biological Chemistry (**1974**), 249(8), 2441-6
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 12 May 1984
AB The physicochem. and biochem. properties of Hb A [**9034-51-9**] associated with haptoglobin were compared with those of Hb bound by antihemoglobin antibody. The mechanism of enhanced peroxidase [9003-99-0] activity of Hb bound by haptoglobin was not activation but **stabilization** of Hb at acidic pH by haptoglobin. Haptoglobin protected Hb from denaturation by acid, and moreover it regenerated denatured Hb at acidic pH. Specific antibody, on the other hand, did not enhance the peroxidase activity of Hb, nor did it prevent the acid denaturation of Hb. H2O2 [7722-84-1]-peroxidase complex, which has not yet been detected in the H2O2-Hb system, was observed in the H2O2-Hb-haptoglobin complex system, indicating that haptoglobin **stabilized** the H2O2-Hb complex. Hb bound by antibody showed a higher affinity for O [7782-44-7]than free Hb, a biphasic Hill plot, slight preservation of heme-heme interaction, and reduced Bohr effect. These characteristic functions of Hb bound by antibody are in striking contrast to those of Hb bound by haptoglobin. Hemes of Hb-antibody complex are not degraded by dithionite under aerobic conditions, whereas those of Hb-haptoglobin complex are degraded, consistent with the view that Hb bound by antibody is **tetrameric**, whereas Hb bound by haptoglobin is dissociated The binding site of Hb for haptoglobin was investigated through immunol. expts. From the data on the immune precipitation reaction of antihemoglobin serum in gels with free Hb, Hb-haptoglobin (human) complex, and Hb-haptoglobin (rabbit) complex, it was apparent that the antigenic determinants of Hb were not modified nor masked and moreover new antigenic determinants of Hb did not appear on complex formation with haptoglobin. These observations suggest that the binding site of Hb for haptoglobin is quite different from that for antihemoglobin antibody.
CC 6-3 (General Biochemistry)
Section cross-reference(s): 15

L122 ANSWER 41 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1973:155177 HCAPLUS
DOCUMENT NUMBER: 78:155177
TITLE: Chemical and biological aspects of the inhibition of red blood cell sickling by cyanate
AUTHOR(S): Manning, James M.; Cerami, Anthony; Gillette, Peter N.; De Furia, Frank G.; Miller, Denis R.
CORPORATE SOURCE: New York Hosp., New York, NY, USA
SOURCE: Advances in Experimental Medicine and Biology (**1972**), 28, 253-60
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB Potassium cyanate [590-28-3] treatment of oxygenated red blood cells from sickle cell anemia patients prevented most of the cells from sickling upon deoxygenation. The cyanate irreversibly carbamylated the NH2-terminal valine residues of the hemoglobin S [**9035-22-7**] mol., and this presumably interfered with the ability of the protein to assume the deoxy conformation. Usually less than 1 carbamyl group per Hb **tetramer** was sufficient to prevent sickling in vitro. Carbamylated Hb S may be **stabilized** in the oxy conformation, this being the reason for the inhibition of sickling.
CC 3-6 (Biochemical Interactions)
Section cross-reference(s): 1

L122 ANSWER 42 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1966:439973 HCAPLUS
DOCUMENT NUMBER: 65:39973

ORIGINAL REFERENCE NO.: 65:7501d-e
TITLE: Stability of sheep-hemoglobin tetramers
AUTHOR(S): Kernohan, J. C.; Johnson, P.
CORPORATE SOURCE: Univ. Cambridge, UK
SOURCE: Biochemical Journal (**1966**), 99(2), 37P-38P
CODEN: BIJOAK; ISSN: 0264-6021
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Apr 2001
AB cf. Adair, J. Biol. Chemical 63, 529(1925). The assumption that sheep hemoglobin on progressive dilution remains predominantly in the tetrameric form has been questioned. However, results of this work lead to the conclusion that the basic assumption of the A. hypothesis (loc. cit) (in which it is assumed that each hemoglobin mol. contains 4 heme groups) is valid for sheep hemoglobin even in the dilute solns. used in kinetic studies of its reactions with ligands.
CC 56 (General Biochemistry)
IT **Hemoglobin**
(**tetramers** of sheep, **stability** of)

L122 ANSWER 43 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1964:455804 HCAPLUS
DOCUMENT NUMBER: 61:55804
ORIGINAL REFERENCE NO.: 61:9713f
TITLE: The role of hemes in the structural integrity of the tetramer of hemoglobin
AUTHOR(S): Banerjee, Ramaprasad; Filitti-Wurmser, Sabine
CORPORATE SOURCE: C.N.R.S., Paris
SOURCE: Compt. Rend. (**1964**), 258(26), 6553-6
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
ED Entered STN: 22 Apr 2001
AB Fragmentation of the hemoglobin mol. by loss of part of the prosthetic groups was demonstrated by ultracentrifugation. It was shown that the home moiety is essential for the maintenance of the structure which permits a tetramer-dimer equilibrium
CC 56 (General Biochemistry)
IT **Hemoglobin**
(structure of, hemes in **stability** of **tetrameric**)

=> d iall abeq tech abex 44-51
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' - CONTINUE? (Y)/N:y

L122 ANSWER 44 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-697293 [66] WPIX
DOC. NO. CPI: C2003-191587
TITLE: Blood substitute product useful to deliver oxygen to a tissue comprises surface-modified oxygenated hemoglobin.
DERWENT CLASS: A96 B04
INVENTOR(S): VANDEGRIFT, K D; WINSLOW, R M; VANDEGRIFF, K D
PATENT ASSIGNEE(S): (VAND-I) VANDEGRIFT K D; (WINS-I) WINSLOW R M; (VAND-I) VANDEGRIFF K D; (SANG-N) SANGART INC
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

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       ZW
US 2003153491   A1 20030814 (200366)          A61K038-42<--
US 2003162693   A1 20030828 (200366)          A61K038-42<--
AU 2003207504   A1 20030730 (200421)          A61K035-12<--
EP 1465643      A1 20041013 (200467)  EN      A61K035-12
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US 6844317      B2 20050118 (200506)          A61K038-00
BR 2003006846   A  20041207 (200507)          A61K035-12
KR 2004081451   A  20040921 (200508)          A61K035-14
US 2005026816   A1 20050203 (200511)          A61K038-42
JP 2005515225   W  20050526 (200535)       36 A61K035-18
US 2005164915   A1 20050728 (200550)#         A61K038-42
CN 1630527      A  20050622 (200563)          A61K035-12
US 6974795      B2 20051213 (200581)          A61K038-00
IN 2004001528   P4 20060210 (200619)  EN      A61K035-12
MX 2004006733   A1 20051201 (200628)          A61K035-12
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APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 2003059363	A1		WO 2003-US696	20030110	<--
US 2003153491	A1	Provisional	US 2002-347741P	20020111	<--
			US 2002-114400	20020401	<--
US 2003162693	A1	Provisional	US 2002-347741P	20020111	<--
		CIP of	US 2002-114400	20020401	<--
			US 2003-340141	20030110	<--
AU 2003207504	A1		AU 2003-207504	20030110	<--
EP 1465643	A1		EP 2003-705713	20030110	<--
			WO 2003-US696	20030110	<--
US 6844317	B2	Provisional	US 2002-347741P	20020111	<--
		CIP of	US 2002-114400	20020401	<--
			US 2003-340141	20030110	<--
BR 2003006846	A		BR 2003-6846	20030110	<--
			WO 2003-US696	20030110	<--
KR 2004081451	A		KR 2004-710847	20040712	
US 2005026816	A1	Provisional	US 2002-347741P	20020111	<--
		CIP of	US 2002-114400	20020401	<--
		Cont of	US 2003-340141	20030110	<--
			US 2004-925067	20040824	
JP 2005515225	W		JP 2003-559525	20030110	<--
			WO 2003-US696	20030110	<--
US 2005164915	A1	CIP of	US 2002-114400	20020401	<--
		CIP of	US 2003-340141	20030110	<--
		Cont of	US 2004-925067	20040824	
			US 2005-88934	20050323	
CN 1630527	A		CN 2003-803648	20030110	<--
US 6974795	B2	Provisional	US 2002-347741P	20020111	<--
		CIP of	US 2002-114400	20020401	<--
		Cont of	US 2003-340141	20030110	<--
			US 2004-925067	20040824	

IN 2004001528	P4	IN 2004-CN1528 WO 2003-US696	20040708	
MX 2004006733	A1	WO 2003-US696 MX 2004-6733	20030110 20040709	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003207504	A1 Based on	WO 2003059363
EP 1465643	A1 Based on	WO 2003059363
BR 2003006846	A Based on	WO 2003059363
JP 2005515225	W Based on	WO 2003059363
US 2005164915	A1 CIP of	US 6844317
US 6974795	B2 Cont of	US 6844317
MX 2004006733	A1 Based on	WO 2003059363

PRIORITY APPLN. INFO: **US 2002-114400 20020401; US 2002-347741P 20020111; US 2003-340141 20030110**; US 2004-925067 20040824; US 2005-88934 20050323

INT. PATENT CLASSIF.:

MAIN: A61K035-12; A61K035-14; A61K035-18; A61K038-00; A61K038-42

SECONDARY: A61K035-144; A61K038-000; A61K038-16; A61K038-166; A61K047-34; A61K047-48; A61P007-08

BASIC ABSTRACT:

WO2003059363 A UPAB: 20031014

NOVELTY - A blood substitute product comprises surface-modified oxygenated hemoglobin having a P50 of less than native stroma-free hemoglobin.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for preparation of the blood substitute product involving:

(a) preparing hemoglobin by oxygenating the hemoglobin having a methemoglobin/total hemoglobin ratio of less than 0.1;

(b) covalently attaching at least one polyalkylene oxide to the hemoglobin to form surface-modified oxygenated hemoglobin having a P50 of less than 10 torr; and

(c) suspending the surface-modified oxygenated hemoglobin in an aqueous diluent.

ACTIVITY - Tranquilizer; Vasotropic; Antibacterial; Immunosuppressive; Cytostatic; Antianemic; Antisickling; Antiparasitic; Hemostatic.

No biological data given.

MECHANISM OF ACTION - None given.

USE - To deliver oxygen to a tissue (claimed), such as in the treatment of trauma, ischemia, hemodilution, septic shock, cancer (in combination with radiotherapy and chemotherapy), chronic anemia, sickle cell anemia, cardioplegia and hypoxia; and for organ perfusion, in cell cultures and to activate hematopoiesis. Also useful for the treatment of livestock and companion animals (e.g. dogs, cats, horses, birds, reptiles) as well as other animals in aquaria, zoos, oceanaria and other facilities that house animals for the treatment of conditions such as equine infectious anemia, feline infectious anemia, hemolytic anemia due to chemicals and other physical agents, bacterial infection, factor IV fragmentation, hypersplenation and splenomegaly, hemorrhagic syndrome in poultry, hypoplastic anemia, aplastic anemia, idiopathic immune hemolytic conditions, iron deficiency, isoimmune hemolytic anemia, microangiopathic

hemolytic and parasitism; and in environments such as emergency rooms, operating rooms, military conflicts, cancer hospitals and veterinary clinics and in blood-type-cross matching and the associated laboratory testing.

ADVANTAGE - The blood substitute product is stable to autooxidation at 24 deg. C, and has high oxygen affinities in an aqueous diluent and a universal applicability. Thus exhibits better stability and superior oxygen carrying properties. The product is capable of delivering oxygen to tissue more efficiently than blood substitutes with oxygen affinities that approximate native hemoglobin.

Dwg.0/10

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V02; B04-B04D2; B04-C03; B04-C03C; B11-B; B14-B02; B14-F02D; B14-F03; B14-G02; B14-H01; B14-J01B; B14-J01B4; B14-N12; B14-S06; B14-S07

TECH UPTX: 20031014

TECHNOLOGY FOCUS - BIOLOGY - Preferred Composition: The product is present in an aqueous medium. The product has a methemoglobin/total hemoglobin ratio of less than 0.1.

Preferred Components: The hemoglobin is a horse hemoglobin. The surface-modified oxygenated hemoglobin has a P50 of less than 10 (preferably less than 7) torr.

Preferred Method: Step (a) further involves isolation of hemoglobin from the red blood cells, having a methemoglobin/total hemoglobin ratio of at least 0.10; and exposing the hemoglobin to the atmosphere for a **time** to lower the methemoglobin/total hemoglobin ratio to less than 0.1. Step (a) is carried out in the absence of a thiol-containing reducing agent.

TECHNOLOGY FOCUS - POLYMERS - Preferred Component: The polyalkylene oxide is polyethylene glycol of formula H(OCH2CH2)nOH.

n = at least 4.

ABEX UPTX: 20031014

ADMINISTRATION - The product is administered in a concentration of 0.1-4 g/dl by intravenous injection.

EXAMPLE - Outdated packed red blood cells were screened for viral infection and subjected to nucleic acid testing. Packed red blood cells were pooled into a sterile vessel, the cell volume and hemoglobin concentration was measured. Leukodepletion was carried out by membrane filtration. The red blood cells were washed with six volumes of 0.9 % sodium chloride at 4 degrees C for the removal of plasma components. Washed red blood cells were lysed at least 4 hours or overnight at 4 degrees C with stirring using water. Lysate was processed in cold to purify hemoglobin by passage through 0.16 micron membrane, and the purified hemoglobin was collected in a sterile depyrogenated vessel. Vial removal was performed by ultrafiltration at 4 degrees C. The purified hemoglobin was exchanged into Ringer's lactate (RL) or phosphate-buffered saline using 10 kD membrane and then concentrated using the same membrane to a final concentration of 1.1-1.5 mM, using RL (pH 7-7.6, 10-12 volumes) at 4 degrees C. The stroma free hemoglobin (SFH) obtained in RL was sterile-filtered through a 0.45-0.2 micron disposable filter capsule and stored at 24 degrees C. Chemical modification of the **hemoglobin** was then performed as follows. The SFH (**tetramer**) in RL (pH 7-7.5) was thiolated by reacting with 10 mM iminothiolane in RL (pH 7-7.5) (ratio of SFH:iminothiolane of 1:10). The thiolated hemoglobin was then polyethylene glycol (PEG)ylated using 20-fold molar excess of Mal-PEG (with an alkyl or phenyl linker) based on starting SFH concentration at 4+/- degrees C. The hemoglobin was first allowed to equilibrate with the atmosphere to oxygenate the hemoglobin. The PEGylated hemoglobin was

processed through a 70-kD membrane to remove excess unreacted reagents or hemoglobin. A 20-volume filtrated was carried out to ensure removal of unreacted reagents, which was monitored by size-exclusion chromatography at 540 and 280 nm. The protein concentration was diluted to 4 g/dl and the pH was adjusted to 7.3 using 0.1 N NaOH. The final Mal-PRG-Hb was sterile filtered using a 0.2 micron sterile disposable capsule and collected into a sterile depyrogenated vessel. The hemoglobin was then diluted to 4 g/dl and the pH was adjusted to 7.4. The composition was then sterile-filtered (0.2 micron) was, aliquoted by weight into sterile glass vials and closed with sterile rubber stoppers crimped seals in a laminar hood and stored at -80 degrees C. The **stability** of the Mal-PRG-**Hb** was determined over 5 days when stored at 4 degrees C. The percentage hemoglobin at 0, 3 and 5 days was 4.8, 5.0 and 4.9 %, respectively.

L122 ANSWER 45 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-383834 [42] WPIX
DOC. NO. CPI: C2002-108200
TITLE: New cross-linked nitrosylated hemoglobin, useful for delivering oxygen to organs, comprises thio-nitrosyl groups on cysteine residues of its globin chains and chemical cross-links between its sub-units..
DERWENT CLASS: B04
INVENTOR(S): KLUGER, R; PEZACKI, J
PATENT ASSIGNEE(S): (KLUG-I) KLUGER R; (PEZA-I) PEZACKI J
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
CA 2309236	A1	20011124	(200242)*	EN	23	C07K014-805<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CA 2309236	A1	CA 2000-2309236	20000524 <--

PRIORITY APPLN. INFO: **CA 2000-2309236**
20000524
INT. PATENT CLASSIF.:
MAIN: C07K014-805
SECONDARY: A61K038-42
BASIC ABSTRACT:
CA 2309236 A UPAB: 20020704
NOVELTY - Cross-linked nitrosylated hemoglobin compries thio-nitrosyl groups on cysteine residues of its globin chains and chemical cross-links between its sub-units.
USE - To deliver oxygen and other substances to organs and tissues of the mammalian body.
ADVANTAGE - The cross-linked nitrosylated **hemoglobin** **stabilizes** its **tetrameric** unit form and prevents its dissociation into units of molecular weight less than 64 kD. This composition is capable of controlling its oxygen release and NO producing properties to predetermined values. This composition does not cause any serious side effects to the patients. No additional reagent is required for generating NO from cross-linked hemoglobin resulting in reducing the risk of unwanted side effects.
Dwg.0/3
FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B04D2
ABEX UPTX: 20020704

SPECIFIC COMPOUNDS - 4 Compounds are specifically disclosed as the cross-linkers e.g. N,N'-5,5'-bis(bis(methylphosphate)isophthalyl)-4,4'-biphenyldiamide.

EXAMPLE - S-Nitrosoglutathione (GSNO) was prepared by acid catalyzed S-nitrosation as follows: mixing thiol (0.1 M) and sodium nitrate (0.1 M) at 4 degrees C with a drop of HCl added to the solution in dark. The solution was stirred and the intense color change was observed. The solution was neutralized using sodium hydroxide (0.1 M), purified and stored at -20 degrees C. Bis-**tetramer** product was prepared by cross-linking **hemoglobin** with cross-linker N,N'-5,5'-bis(bis(methylphosphate)isophthalyl)-4,4'-biphenyldiamine (MPIB) at pH 8 for 16 hours at 25 degrees C and isolated by size exclusion chromatography. S-nitrosylation of beta-cys93 side chains of oxygenated hemoglobin (oxyHbs) was performed using GSNO and by treatment with acidified sodium nitrite followed by purification. Oxygen binding experiment was performed by exposing oxyHb to a constant flow of nitrogen and exposing deoxyHb to a constant flow of oxygen. The samples experienced a concentration gradient as the solution became oxygenated or deoxygenated and absorbance of the samples at 560 nm were recorded as a function of measured oxygen partial pressure in each run. The oxygen binding properties of cross-linked HbSNO for cycle 6 was P50 = 6.5; and n50 = 1. The results of the oxygen binding studies showed that one can control the oxygen affinity of products by selection of cross-linking reagent.

L122 ANSWER 46 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-611596 [58] WPIX
DOC. NO. CPI: C2000-183037
TITLE: Composition with oxygen transporting capability comprises oxygen transporting molecules bonded to antioxidants, specifically hemoglobin-antioxidant composition useful e.g. in ischemic tissue reperfusion.
DERWENT CLASS: A96 B05
INVENTOR(S): ADAMSON, G W; MCINTOSH, G A; ADAMSON, J G
PATENT ASSIGNEE(S): (HEMO-N) HEMOSOL INC; (HEMO-N) HEMOSOL LP
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2000056367	A1	20000928	(200058)*	EN	40	A61K047-48<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
CA 2266174	A1	20000918	(200062)	EN		C07K014-805<--
AU 2000032690	A	20001009	(200103)			A61K047-48<--
EP 1163010	A1	20011219	(200206)	EN		A61K047-48<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
KR 2001111571	A	20011219	(200238)			A61K047-48<--
JP 2002540081	W	20021126	(200307)		38	A61K038-16<--
NZ 513933	A	20030926	(200366)			A61K047-48<--
AU 782407	B2	20050728	(200553)			A61K047-48
US 6974794	B1	20051213	(200581)			A61K037-14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2000056367	A1	WO 2000-CA299	20000320	<--
CA 2266174	A1	CA 1999-2266174	19990318	<--
AU 2000032690	A	AU 2000-32690	20000320	<--
EP 1163010	A1	EP 2000-910473	20000320	<--
		WO 2000-CA299	20000320	<--
KR 2001111571	A	KR 2001-711246	20010904	<--
JP 2002540081	W	JP 2000-606271	20000320	<--
		WO 2000-CA299	20000320	<--
NZ 513933	A	NZ 2000-513933	20000320	<--
		WO 2000-CA299	20000320	<--
AU 782407	B2	AU 2000-32690	20000320	<--
US 6974794	B1	WO 2000-CA299	20000320	<--
		US 2002-926167	20020108	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000032690	A	Based on	WO 2000056367
EP 1163010	A1	Based on	WO 2000056367
JP 2002540081	W	Based on	WO 2000056367
NZ 513933	A	Based on	WO 2000056367
AU 782407	B2	Previous Publ.	AU 2000032690
		Based on	WO 2000056367
US 6974794	B1	Based on	WO 2000056367

PRIORITY APPLN. INFO: **CA 1999-2266174**
19990318

INT. PATENT CLASSIF.:
MAIN: A61K037-14; A61K038-16; A61K047-48; C07K014-805
SECONDARY: A61K031-05; A61K031-739; A61K038-42; A61P007-06; A61P007-08

BASIC ABSTRACT:

WO 200056367 A UPAB: 20001114

NOVELTY - NOVELTY

A chemical composition has oxygen transporting capability and comprises biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from e.g. non-enzymatic phenolic compounds, pyrazolines, carotenoid and retinoid compounds.

DETAILED DESCRIPTION - A chemical composition has oxygen transporting capability and comprises biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from non-enzymatic phenolic compounds, pyrazolines, carotenoid and retinoid compounds, quinones, tetrapyrroles, indoles and aminoindoles, purine analogs, ascorbic acid, and steroid and alkaloid antioxidants.

INDEPENDENT CLAIMS are also included for the following:

(1) a process for preparing a hemoglobin composition having antioxidant properties;

(2) use of a chemical composition as above in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients.

ACTIVITY - Antioxidant.

The degree of antioxidant protection by Hb-Trolox conjugates was compared to controls. Red blood cell lysis in the presence of free Trolox, free (control) hemoglobin, a mixture of free Trolox and hemoglobin, or

hemoglobin Trolox conjugate was measured. Results showed that both the Trolox and hemoglobin, alone, exhibited less protection than the corresponding hemoglobin-Trolox conjugates. The mixture of free Trolox and hemoglobin showed greater protection than an equal concentration of either compound alone, but still less protection than the corresponding hemoglobin-Trolox conjugates. Since the conjugate and the mixture had the same hemoglobin content, and the conjugate contained the same or less Trolox than the mixture, the greater activity of the conjugate suggested a synergistic effect, indicated by an increase in overall antioxidant activity due to conjugation.

USE - As hemoglobin-antioxidant compositions for administration to living beings for oxygen-transport purposes and antioxidant therapeutic purposes. The compositions may be used during temporary interruption of blood flow to tissue in surgical procedures e.g. cardiac surgery and organ preservation or transplantation. For reperfusion of ischemic tissue in blocked blood vessels in disease events such as myocardial infarction, thrombotic stroke, embolic vascular occlusions, angina pectoris and peripheral vascular insufficiency.

ADVANTAGE - The conjugation of extracellular hemoglobin to the antioxidant prevents oxygen-hemoglobin reactions that generate Met-hemoglobin and the oxygen free radical, superoxide (.O2-) which causes tissue damage, e.g. reperfusion injury. (This does not occur inside the red blood cell due to the presence of enzymes such as superoxide dismutase and catalase which convert superoxide to harmless by-products, water and oxygen). The oxidized antioxidant moiety conjugated to the hemoglobin may be reduced in vivo to a chemical state in which it is capable of further antioxidant activity and the conjugate recycled in the body for further action.

Dwg.0/4

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V01; B03-A; B03-F; B04-A07A; B04-B04D2; B06-D01; B06-D09; B06-D18; B07-D08; B10-A06; B10-E02; B10-H01; B14-F05; B14-F11; B14-S08

TECH UPTX: 20001114

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Oxygen-transporting Substance: The oxygen transporting substance is a heme-protein macromolecule, especially a hemoglobin species. The hemoglobin of the conjugate is modified by a cross-linking agent. The **hemoglobin** is at least partially **stabilized** by the cross-linking agent to form **stabilized tetrameric** units. The **hemoglobin** of the conjugate is at least partially **oligomerized** into **oligomers** of up to 12 stabilized tetrameric units.

Preferred Antioxidant: The antioxidant is a phenolic compound containing one or more groups of formula (I) and is especially (i) a polyphenolic, a substituted phenolic or a phenolic ether; (ii) a di-t-butylhydroxyphenylthio-substituted hydroxamic acid; (iii) a chroman-based compound such as a chromanol or a dihydrobenzofuranol; (iv) a flavanoid or isoflavanoid such as flavonone and dihydroflavanol; (v) a gallate; (vi) a catechol or catechol derivative; or (vii) a phenolic acid. The phenolic antioxidant is preferably a chromanol. The composition comprises the reaction product of an oxygen transporting compound and a 6-hydroxy chroman compound having antioxidant properties of formula (II), especially of formula (II').

n = 1-3.

In (I), the aromatic ring is optionally further substituted and optionally fused or linked to another carbocyclic or heterocyclic ring system.

R1-R3 = H, 1-8C alkyl or (CH2)n'X;

n' = 0-20;

R, R4-R6 = H, 1-20C alkyl, X or (CH2)mX;
X = a substituent containing a reactive functional group selected in conjunction with the chosen oxygen transporting compound so as to be capable of reacting with it to effect a chemical linkage of the oxygen transporting compound to the chroman compound;
provided that the chroman compound includes at least one functional group X;
R' = H or 1-20C alkyl;
R1'-R3'= H or 1-4C alkyl;
R4' = a bond or 1-8C alkyl.
Preferably, X contains a functional group capable of reacting with amino acid residues of the protein chains of the heme protein macromolecule.
Especially X = halo, carboxyl, amino, hydroxyl, thiol, azide, azo, aldehyde or phosphate.
Preferably at least on of R1-R3 is methyl and R4 = a bond.
Preferred Composition: The composition is a covalently linked conjugate of the chroman compound and human **hemoglobin.** The composition comprises a mixture of **tetrameric stabilized hemoglobin** units conjugated to the chroman carboxylic acid antioxidant and **oligomers** of 2-8 such **stabilized hemoglobin** units conjugated to the chroman carboxylic acid antioxidant.
Preparation: In (1), the method comprises chemically reacting hemoglobin and a hydroxy chroman compound as above (i.e.(II)) to form its covalently linked chemical conjugate. Preferably, prior to conjugation to the chroman carboxylic acid, the hemoglobin is reacted with a cross-linking reagent. The hemoglobin-chroman carboxylic acid conjugate is subsequently reacted with a hemoglobin cross-linking reagent, especially a polyaldehyde, particularly oxidatively ring opened-raffinose (o-raffinose). The **hemoglobin** is at least partially **oligomerized** by further reaction with o-raffinose. The reaction between **hemoglobin** and the hydroxy chroman compound is conducted in the presence of an activating compound. The activating compound is a carbodiimide, particularly 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) and the chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol (Trolox) (Ia).

TECHNOLOGY FOCUS - **POLYMERS** - The **hemoglobin** is modified or cross-linked with a polyaldehyde, glutaraldehyde, a diaspirin compound, a pyridoxyl compound or a trimesoyl compound. Preferably the hemoglobin is crosslinked with a polyaldehyde derived from oxidative ring-opening of a polysaccharide. The polysaccharide is especially raffinose. The **hemoglobin**-antioxidant conjugate is bonded to a biocompatible **polymer.** The biocompatible **polymer** is polyethylene glycol, a polysaccharide, a polyamino acid, or an insoluble support.

ABEX UPTX: 20001114
SPECIFIC COMPOUNDS - The chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol. (Ia)
EXAMPLE - A series of experiments was conducted in which Trolox (TX) was conjugated to carbonmonoxyhemoglobin (COHb) using EDC as a coupling agent under conditions set out in a table. In each case, EDC, EDC and Trolox (TX) were combined in equimolar concentration in acetonitrile for 10 minutes at room **temperature** to give a stock TX-EDC solution (1.55 M). The TX-EDC solution was diluted with acetonitrile, when necessary, just prior to addition to Hb so that the final acetonitrile and TX-EDC content of the conjugation reaction was as indicated in the table (10 volume% in 8 cases and 1 volume % in 1 case). All conjugations were done in 40-50 mM MES buffer at pH 7 in 8 cases and pH 4 in one case. Reaction mixtures were held at 22 degreesC for up to 24 hours under CO

gas. Samples were filtered and dialyzed against phosphate-buffered saline (PBS), pH 7.4.
Hemoglobin-TX conjugates prepared as above were dialyzed against 50 mM Bis-Tris buffer, pH 6.8. 3 Equivalents o-raffinose dissolved in water were added to solutions of hemoglobin-Trolox to give a final hemoglobin concentration of 42 mg/ml. The mixtures were held under CO gas at 22 degreesC for 24 hours. The solutions were made 30 mM in sodium acetate, and 20 equivalents of aqueous dimethylamine borane relative to o-raffinose content were added. After 24 hours, the solutions were dialyzed against water, then PBS pH 7.4. Size exclusion chromatography indicated formation of intra- and intermolecularly cross-linked hemoglobin-TX species. If necessary, non-crosslinked hemoglobin species were removed by conventional means, e.g. ultrafiltration.

L122 ANSWER 47 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-447404 [41] WPIX
CROSS REFERENCE: 1995-301549 [39]; 1997-086694 [08]; 1997-372091 [34]; 1997-557584 [51]; 1998-119490 [11]; 1998-216563 [19]; 1999-166732 [14]; 1999-429264 [36]
DOC. NO. CPI: C1997-142645
TITLE: Allosteric modification of haemoglobin to low oxygen-affinity state in blood - using material such as 2-[4-[[(3,5-di chloro-anilino)carbonyl]methyl]phenoxy]-2-methyl-propionic acid, which is active even in presence of serum albumin.
DERWENT CLASS: B05
INVENTOR(S): ABRAHAM, D J; POYART, C
PATENT ASSIGNEE(S): (UYVI-N) UNIV VIRGINIA COMMONWEALTH
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5661182	A	19970826	(199741)*		14	A61K031-245<--

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
US 5661182	A	CIP of	US 1990-478848	19900212	<--
		Cont of	US 1990-623346	19901207	<--
		CIP of	US 1991-702947	19910520	<--
		CIP of	US 1991-722382	19910626	<--
		CIP of	US 1993-6246	19930119	<--
		CIP of	US 1993-101501	19930730	<--
		Cont of	US 1993-127587	19930928	<--
			US 1995-478108	19950607	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5661182	A	CIP of	US 5049695
		CIP of	US 5122539
		CIP of	US 5290803
		CIP of	US 5382680
		CIP of	US 5432191

PRIORITY APPLN. INFO: **US 1993-127587 19930928; US**

1990-478848 19900212;
US 1990-623346
19901207; US
1991-702947 19910520;
US 1991-722382
19910626; US 1993-6246
19930119; US
1993-101501 19930730;
US 1995-478108
19950607

INT. PATENT CLASSIF.:
MAIN: A61K031-245
SECONDARY: A61K031-195; A61K031-325; C07C045-00

BASIC ABSTRACT:

US 5661182 A UPAB: 19990908

Allosterically modifying haemoglobin (Hb) towards a low oxygen affinity state in blood comprises:

(a) providing blood with a allosteric effector molecule (AEM), and

(b) permitting the AEM to penetrate into erythrocytes in the blood and bind to Hb in the blood.

The AEM binds to only one pair of symmetry related sites in the central water cavity of Hb at the Lys 99 alpha , Arg 141 alpha and Asn 108 beta residues, each pair of symmetry related sites having residues on three separate sub-units of the **Hb**. The AEM **stabilises** the **Hb** in a lower oxygen affinity state, and is active in the presence of normal concentrations of serum albumin (SA) in the blood. The AEM maintains > 60% of its activity, in terms of right shifting the oxygen dissociation curve of Hb for a buffered red cell suspension at pH 7.4, in 140 mM NaCl and 50 mM bis-Tris buffer at 37 deg. C, which contains 20-25 mu M of **Hb** on a **tetramer** basis, 50 mu M SA and 0.5 mM of the AEM, relative to the buffered suspension without 50 mu M SA.

The AEM retains > 80% of its activity, in terms of a calculated oxygen delivery index for the buffered suspension containing 50 mu M SA, relative to the buffered suspension without 50 mu M SA.

USE - Agents which can allosterically modify Hb towards a lower oxygen affinity state have potential for use in many clinical applications, e.g. in treatment of ischaemia, heart disease, wounds, Alzheimer's disease, depression, schizophrenia, ARDS, shock and polycythemia, as radiosensitising agents or for extending the shelf-life of blood.

ADVANTAGE - The AEM is either not bound by SA or only interacts to a small extent with SA, and is thus active in whole blood and in vivo.

When used in vivo, prior art compounds, such as bezafibrate, are bound in vivo by SA and thus are not able to reach red cells, cross the red cell membrane, and interact with Hb to produce the desired effect.

Dwg.0/6

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B04D2; B04-B04D5; B10-D03; B12-M06; B14-F01B; B14-F02; B14-J01; B14-N17A

L122 ANSWER 48 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1993-167403 [20] WPIX
CROSS REFERENCE: 1990-361480 [48]; 1993-167626 [20]; 1997-052322 [05]
DOC. NO. CPI: C1993-074747
TITLE: New conjugate of drug and **haemoglobin** or analogues - used for controlled release to blood, with better **stability** and longer half life, especially for peptide(s) e.g. angiotensin.
DERWENT CLASS: B04 B07 C03 C07 P34

INVENTOR(S): ANDERSON, D C; MATHEWS, A J; STETLER, G L; ANDERSEN, D C; HOFFMAN, S J; LOOKER, D L; NAGAI, K; ROSENDAHL, M S; WAGENBACH, M

PATENT ASSIGNEE(S): (HEMO-N) HEMOSOL INC; (SOMA-N) SOMATOGEN INC

COUNTRY COUNT: 40

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9308842	A1	19930513	(199320)*	EN	54	A61K047-48<--
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE						
W: AT AU BB BG BR CA CH CS DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO PL RO RU SD SE UA US						
AU 9331324	A	19930607	(199338)			<--
EP 611306	A1	19940824	(199433)	EN		<--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE						
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JP 07500840	W	19950126	(199513)			A61K047-48<--
JP 07501059	W	19950202	(199514)			C07K014-805<--
AU 665599	B	19960111	(199609)			A61K047-42<--
US 5545727	A	19960813	(199638)		130	C12N015-12<--
US 5679777	A	19971021	(199748)		42	A61K035-14<--
US 5744329	A	19980428	(199824)		133	C12P021-06<--
SG 47882	A1	19980417	(199827)			C07K015-00<--
US 5759517	A	19980602	(199829)			A61K051-00<--
EP 611306	B1	19980708	(199831)	EN		<--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE						
DE 69225978	E	19980723	(199835)			C07K014-00<--
EP 857489	A2	19980812	(199836)	EN		<--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE						
DE 69226197	E	19980813	(199838)			<--
US 5798227	A	19980825	(199841)			C12P021-06<--
US 5801019	A	19980901	(199842)			C12P021-06<--
US 5844088	A	19981201	(199904)			C07K014-805<--
US 5844089	A	19981201	(199904)			C07K014-805<--
US 6274331	B1	20010814	(200148)			G01N033-53<--
JP 3426599	B2	20030714	(200347)		18	A61K047-48<--
CA 2122717	C	20030715	(200353)	EN		C07K014-805<--

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE	
WO 9308842	A1		WO 1992-US9713	19921106	<--
AU 9331324	A		AU 1993-31324	19921106	<--
EP 611306	A1		EP 1992-925154	19921106	<--
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FI 9402138	A		WO 1992-US9752	19921106	<--
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JP 07500840	W		WO 1992-US9713	19921106	<--
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		CIP of	US 1991-671707	19910401	<--
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US 5679777	A	CIP of	US 1991-789177	19911108	<--

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US 5744329	A	CIP of	US 1989-349623	19890510	<--
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			US 1995-444942	19950519	<--
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US 5759517	A	CIP of	US 1991-789177	19911108	<--
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EP 611306	B1		EP 1992-925154	19921106	<--
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DE 69225978	E		DE 1992-625978	19921106	<--
			EP 1992-925173	19921106	<--
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DE 69226197	E		DE 1992-626197	19921106	<--
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US 5798227	A	CIP of	US 1989-349623	19890510	<--
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US 5801019	A	CIP of	US 1989-349623	19890510	<--
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US 5844088	A	CIP of	US 1989-349623	19890510	<--
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		Div ex	WO 1990-US2654	19900510	<--
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US 5844089	A	CIP of	US 1989-349623	19890510	<--
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		CIP of	US 1989-379116	19890713	<--
		Div ex	WO 1990-US2654	19900510	<--
		CIP of	US 1991-671707	19910401	<--
		Div ex	US 1991-789179	19911108	<--
			US 1995-450733	19950525	<--
US 6274331	B1	CIP of	US 1989-349623	19890510	<--
		CIP of	US 1989-374161	19890630	<--
		CIP of	US 1989-379116	19890713	<--
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		Div ex	US 1991-789179	19911108	<--

		US 1995-444915	19950519	<--
JP 3426599	B2	WO 1992-US9713	19921106	<--
		JP 1993-508781	19921106	<--
CA 2122717	C	CA 1992-2122717	19921106	<--
		WO 1992-US9713	19921106	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9331324	A Based on	WO 9308842
EP 611306	A1 Based on	WO 9308842
JP 07500840	W Based on	WO 9308842
JP 07501059	W Based on	WO 9309143
AU 665599	B Previous Publ.	AU 9331324
	Based on	WO 9308842
US 5679777	A CIP of	US 5545727
	Based on	WO 9308842
US 5744329	A Div ex	US 5545727
US 5759517	A CIP of	US 5545727
EP 611306	B1 Based on	WO 9308842
DE 69225978	E Based on	EP 611376
	Based on	WO 9309143
EP 857489	A2 Div ex	EP 611376
DE 69226197	E Based on	EP 611306
	Based on	WO 9308842
US 5798227	A Div ex	US 5545727
US 5801019	A Div ex	US 5545727
US 5844088	A Div ex	US 5545727
US 5844089	A Div ex	US 5545727
US 6274331	B1 Div ex	US 5545727
JP 3426599	B2 Previous Publ.	JP 07500840
	Based on	WO 9308842
CA 2122717	C Based on	WO 9308842

PRIORITY APPLN. INFO: **US 1991-789179 19911108; US 1991-789177 19911108; US 1989-349623 19890510; US 1989-374161 19890630; US 1989-379116 19890713; US 1991-671707 19910401; US 1994-240711 19940712; WO 1990-US2654 19900510; US 1995-444942 19950519; US 1995-457753 19950601; US 1995-446105 19950519; US 1995-444939 19950519; US 1995-444991 19950519; US 1995-450733 19950525; US 1995-444915 19950519**

REFERENCE PATENTS: 2.Jnl.Ref; WO 9013645; WO 9108220; 6.Jnl.Ref; EP 290252; EP 402300; WO 8809179; WO 9116349; WO 9211283

INT. PATENT CLASSIF.:
MAIN: A61K035-14; A61K047-42; A61K047-48; A61K051-00; C07K000-00; C07K014-00; C07K014-805; C07K015-00; C12N015-12; C12P021-06; G01N033-53
SECONDARY: A61K038-00; A61K038-16; A61K039-385; A61K049-02; A61M036-14; C07H017-00; C07K001-10; C12N001-20; C12N015-09; C12P021-04

BASIC ABSTRACT:
WO 9308842 A UPAB: 20030820
New conjugate (A) of a drug (I), other than albumin, and a haemoglobin-like protein (II) can release active (I) under physiological conditions.

Pref. (I) is covalently bonded to (II), especially directly or indirectly to a Cys residue. (II) may be a nutein of normal human haemoglobin with altered O2 affinity, increased intravascular retention or inhibited haptoglobin binding; or it is a pseudo oligomer with 2 or more globin-like domains which is asymmetrically mutated to provide a single additional crosslinkable Cys for attachment to (I).

The Cys residue to which (I) is attached is e.g. a mutation of a non-Cys residue in alpha or beta globin, or it may reside in the crevice in oxy or deoxy form. If attached via a disulphide, the Cys residue is in a region where approach of endogenous reduced agents is electrostatically or sterically hindered. Peptides drug may be derivatised to provide an SH gp. for crosslinking to Cys and modified to improve disulphide bond stability. Also suitable as (I) are synthetic drugs; nucleic acids; polymers; herbicides or pesticides (for use on plants), etc.

(A) are incorporated into tablets, capsules, injectable solns. etc. and the dose is usually enough to provide a concentration in the blood of InM-ImM.

USE/ADVANTAGE - (A) are especially used for controlled release into the blood of (I) with intravascular half life less than that of (II), partic. a peptide vasoconstrictive or vasodilating agent e.g. angiotensin II or atrial natriunetic factor. Conjugation to (II) stabilises (I); extends their half-like and improves retention in the blood stream. (A) may provide simultaneous release of (I) and O2 (some (I), e.g. antitumour agents, are more effective in presence of O2). The use of (A) as imaging agents, e.g. where (I) is 99m-Tc, is also contemplated.

Dwg.0/0

FILE SEGMENT: CPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B04D2; B04-B04D3; B04-C01B; B12-F06; B12-F07

ABEQ US 5545727 A UPAB: 19960924
A DNA molecule comprising a DNA sequence coding on expression for non-naturally occurring, genetically fused, pseudodimeric di-alpha globin-like polypeptide consisting essentially of two and only two alpha globin-like domains, connected either directly by one peptide bond or by a peptide linker of 1-5 amino acids into a single unbranched polypeptide chain, said chain being capable of associating with beta globin and incorporating heme to form a **pseudotetrameric hemoglobin** -like protein with reversible oxygen binding activity.

Dwg.0/36

ABEQ US 5679777 A UPAB: 19971209
A conjugate of (a) a drug of interest, other than albumin, and (b) a hemoglobin-like protein,

where the conjugate (1) has a therapeutic activity, as a conjugate, which is attributable to said drug, and/or (2) is capable of releasing the drug in therapeutically active form under physiological conditions,

and where at least one of the following conditions applies:

(I) the hemoglobin-like protein is not identical to human hemoglobin AO or human hemoglobin S, or

(II) the drug of interest
(a) is not ethacrynic acid, bezafibrate, succinyl-L-tryptophan-L-tryptophan, p-bromobenzyloxyacetic acid, or polyethylene glycol or
(b) is bound through a disulfide to a cysteine residue of the hemoglobin-like protein.
Dwg.0/0

L122 ANSWER 49 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-217022 [26] WPIX
DOC. NO. CPI: C1992-098282
TITLE: Imido ester crosslinked **haemoglobin** compsn. used as oxygen carrier - has satisfactory P50, and is **stable** to dissociation or oxidation.
DERWENT CLASS: B04
INVENTOR(S): GARLICK, R L; LYLE, S B; MARTIN, J P; LYLE, S
PATENT ASSIGNEE(S): (UPJO) UPJOHN CO
COUNTRY COUNT: 56
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9209630	A1	19920611	(199226)*	EN	23	C07K015-00<--
RW: AT BE BF BJ CF CG CH CI CM DE DK ES FR GA GB GN GR IT LU ML MR NL SE SN TD TG						
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AU 9185466	A	19920625	(199239)			C07K015-00<--
PT 99666	A	19921030	(199247)			A61K035-00<--
NZ 240377	A	19930127	(199310)			A61K037-02<--
FI 9302461	A	19930528	(199330)			C07K000-00<--
ZA 9108348	A	19930630	(199331)		20	C08H000-00<--
NO 9301956	A	19930528	(199336)			A61K037-14<--
EP 559655	A1	19930915	(199337)	EN		C07K015-00<--
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE						
HU 64571	T	19940128	(199409)			C07K015-22<--
CZ 9300854	A3	19940216	(199414)			C07K015-00<--
JP 06502848	W	19940331	(199418)		9	C07K015-22<--
SK 9300549	A3	19931006	(199420)			C07K015-00<--
AU 650287	B	19940616	(199429)			A61K037-14<--
US 5362855	A	19941108	(199444)		9	C07C233-00<--
EP 559655	B1	19950315	(199515)	EN	15	C07K014-805<--
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE						
DE 69108258	E	19950420	(199521)			C07K014-805<--
ES 2069908	T3	19950516	(199526)			C07K014-805<--
US 5521154	A	19960528	(199627)		9	A61K038-00<--
IL 99785	A	19960514	(199633)			C07K014-805<--
IE 68169	B	19960529	(199640)			C07K015-00<--
CZ 281912	B6	19970312	(199717)			C07K014-805<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 9209630	A1	WO 1991-US7155	19911003	<--
AU 9185466	A	AU 1991-85466	19911003	<--
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NZ 240377	A	NZ 1991-240377	19911029	<--
FI 9302461	A	WO 1991-US7155	19911003	<--
		FI 1993-2461	19930528	<--
ZA 9108348	A	ZA 1991-8348	19911018	<--

NO 9301956	A		WO 1991-US7155	19911003	<--
			NO 1993-1956	19930528	<--
EP 559655	A1		EP 1991-917174	19911003	<--
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HU 64571	T		WO 1991-US7155	19911003	<--
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CZ 9300854	A3		CZ 1993-854	19911003	<--
JP 06502848	W		JP 1991-516187	19911003	<--
			WO 1991-US7155	19911003	<--
SK 9300549	A3		SK 1993-549	19930528	<--
AU 650287	B		AU 1991-85466	19911003	<--
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		Cont of	WO 1991-US7155	19911003	<--
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EP 559655	B1		EP 1991-917174	19911003	<--
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DE 69108258	E		DE 1991-608258	19911003	<--
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ES 2069908	T3		EP 1991-917174	19911003	<--
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		Cont of	US 1993-65170	19930520	<--
			US 1994-260173	19940615	<--
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IE 68169	B		IE 1991-4144	19911128	<--
CZ 281912	B6		WO 1991-US7155	19911003	<--
			CZ 1993-854	19911003	<--

FILING DETAILS:

PATENT NO	KIND		PATENT NO
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EP 559655	A1	Based on	WO 9209630
HU 64571	T	Based on	WO 9209630
JP 06502848	W	Based on	WO 9209630
AU 650287	B	Previous Publ.	AU 9185466
		Based on	WO 9209630
EP 559655	B1	Based on	WO 9209630
DE 69108258	E	Based on	EP 559655
		Based on	WO 9209630
ES 2069908	T3	Based on	EP 559655
US 5521154	A	Cont of	US 5362855
CZ 281912	B6	Previous Publ.	CZ 9300854
		Based on	WO 9209630

PRIORITY APPLN. INFO: **US 1990-619840 19901129; US 1993-65170 19930520; US 1994-260173 19940615**

REFERENCE PATENTS: 4.Jnl.Ref; EP 181033; EP 195558; EP 361720; US 4053590; 02Jnl.Ref

INT. PATENT CLASSIF.:

MAIN: A61K035-00; A61K037-02; A61K037-14; A61K038-00; C07C233-00; C07K000-00; C07K014-805; C07K015-00; C07K015-22; C08H000-00

SECONDARY: A61K037-00; A61K038-42; C07K003-08; C07K003-12; C07K013-00; C07K015-06; C08H001-00

BASIC ABSTRACT:

WO 9209630 A UPAB: 19931006
A cross-linked haemoglobin (Hb) compsn. useful for transporting oxygen to living cells, comprising **Hb** free of impurities predominantly in **tetramer** form cross-linked with an imido ester, and having a P50 of at least 13 mm Hg, is new.

The imido ester is pref. dimethyl adipimidate (DMA) or dimethyl suberimidate. The prod. cross-linked Hb has at least 80, more pref. 95% of material with M.weight at least 64000. The purified Hb lysate is most pref. deoxygenated, and is reacted with the imido-ester at pH 8-12 in a solution containing Tris-HCl buffer and opt. NaCl, most pref. 50 mM Tris-HCl and 0.1-2M NaCl. Repeated treatments are opt. used. Low m.weight Hb cpds. are then removed by size exclusion, especially by chromatography.

USE/ADVANTAGE - The prod. is a blood substitute for use in transfusions in humans and animals, or as an oxygen carrying fluid for analytical, transplant, or laboratory usage. It contains little or no high M.weight molecules to cause compliment activation, or low M.weight molecules to be passed into the renal tubules. The cross-linking **stabilises** dissociation into **Hb** dimers and oxidation at physiological **temperature** and results are superior to those with glutaraldehyde cross-linked Hb. The imido-esters are readily available and reaction occurs specifically and rapidly under mild conditions to provide cross-linking. For use, the compsn. is diluted with sterile water or saline, to a concentration of 40-140 mg/ml.
0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B04-B04D2; B10-A20; B12-H06

ABEQ ZA 9108348 A UPAB: 19931118
An imidoester, crosslinked haemoglobin composition useful in the transport of oxygen to living cells and being essentially free of any impurities, a P50 of at least 13mm Hg and predominantly in tetramer form.

Pref., the crosslinked haemoglobin composition has a predominant mol.wt. of at least 64,000.

USE/ADVANTAGE - The purified and crosslinked **haemoglobin** has improved crosslink **stability** to autoxidation and can be used as a blood substitute for mammals or as an oxygen transport fluid.
Dwg.0/0

ABEQ EP 559655 A UPAB: 19931123
A crosslinked haemoglobin (Hb) compsn. useful for transporting oxygen to living cells, comprising **Hb** free of impurities predominantly in **tetramer** form cross-linked with an imido ester, and having a P50 of at least 13 mm Hg, is new.

The imido ester is pref. dimethyl adipimidate (DMA) or dimethyl suberimidate. The prod. cross-linked Hb has at least 80, more pref. 95% of material with M.wt. at least 64000. The purified Hb lysate is most pref. deoxygenated, and is reacted with the imido-ester at pH 8-12 in a soln. contg. Tris-HCl buffer and opt. NaCl, most pref. 50 mM Tris-HCl and 0.1-2M NaCl. Repeated treatments are opt. used. Low m.wt. Hb cpds. are then removed by size exclusion, esp. by chromatography.

USE/ADVANTAGE - The prod. is a blood substitute for use in transfusions in humans and animals, or as an oxygen carrying fluid for analytical, transplant, or laboratory usage. It contains little or no high M.wt. mols. to cause compliment activation, or low mol. wt. mols. to be passed into the renal tubules. The crosslinking **stabilises** dissociation into **Hb** dimers and oxidn. at physiological **temp.** and results are superior to those with glutaraldehyde crosslinked Hb. The imido-esters are readily available and reaction occurs specifically and rapidly under mild conditions to provide crosslinking. For use, the compsn. is diluted with sterile water or saline, to a concn. of 40-140 mg/ml

ABEQ US 5362855 A UPAB: 19941223
Prepn. of crosslinked haemoglobin for transporting O2 to living cells comprises crosslinking a purified haemoglobin lysate with dimethyl adipimidate or dimethyl suberimidate at a pH of at least 8.0 in a **polymerisation** soln. cotng. TRIS-HCl buffer. At least 80% of the **haemoglobin** has a mol.wt. of 64 kD and a P50 of at least 13.
The **polymerisation** soln. includes NaCl. The purified **haemoglobin** lysate is deoxygenated. **Haemoglobin** has improved **stability** to autoxidn.
Dwg.0/0

ABEQ EP 559655 B UPAB: 19950425
Hemoglobin which is essentially free of impurities; is cross-linked with a bifunctional imidoester; is more **stable** to methemoglobin formation that the unmodified **hemoglobin**; is predominantly in **tetramer** form; and has a P50, i.e. an oxygen partial pressure at half saturation, of at least 1.7 kPa (13 mm Hg) at pH 7.4.
Dwg.0/0

ABEQ US 5521154 A UPAB: 19960710
A cross-linked haemoglobin for transporting oxygen in living cells having a P50 of at least 13 and wherein at least 80% of said haemoglobin has a molecular weight of at least 64,000 made by the process comprising:
cross-linking a deoxygenated **haemoglobin** lysate with dimethyl adipimidate or dimethyl suberimidate in a **polymerization** solution having a pH of at least 8 and comprising 50 nM Tris-HCl, NaCl and a buffer selected from the group consisting of 2-amino-2-methyl-1-propanol, Tris, sodium carbonate, CHES and CAPSO.
Dwg.0/0

L122 ANSWER 50 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1985-123939 [21] WPIX
DOC. NO. CPI: C1985-053758
TITLE: Non-covalent haemoglobin conjugates - useful as blood substitutes.
DERWENT CLASS: A96 B04
PATENT ASSIGNEE(S): (BINT) BRAUN MELSUNGEN AG B; (INTG) INTERMEDICAT GMBH
COUNTRY COUNT: 17
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC	
EP 142125	A	19850522	(198521)*	GE	26		<--
R: AT BE CH DE FR GB IT LI LU NL SE							
DE 3340592	A	19850523	(198522)				<--
NO 8404494	A	19850603	(198529)				<--
JP 60123425	A	19850702	(198532)				<--
FI 8404331	A	19850511	(198533)				<--
DK 8405349	A	19850511	(198535)				<--
ES 8607731	A	19861116	(198704)				<--
US 4698387	A	19871006	(198742)				<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
EP 142125	A	EP 1984-113405	19841107	<--
DE 3340592	A	DE 1983-3340592	19831110	<--
JP 60123425	A	JP 1984-237409	19841110	<--
ES 8607731	A	ES 1984-537507	19841108	<--
US 4698387	A	US 1984-665354	19841026	<--

PRIORITY APPLN. INFO: **DE 1983-3340592**
19831110
REFERENCE PATENTS: 3.Jnl.Ref; A3...8622; No-SR.Pub
INT. PATENT CLASSIF.: A61K031-71; A61K037-14; C07C103-52; C07G007-00; C07K015-00; C07K017-02; C08B037-00; C08F261-04; C08G065-00; C08L089-06

BASIC ABSTRACT:

EP 142125 A UPAB: 19930925

New haemoglobin conjugates (I) comprise a water-soluble carrier (II) linked noncovalently and reversibly via an anionic ligand (III) to the allosteric binding centre of purified human haemoglobin A (IV), where(IV) is free of endogenous ligands.

(II) has a molecular weight of 400-500,000 and is selected from polyvinylpyrrolidone and its derivs., dextran and its derivs., polyvinyl alcohol, polysaccharides, soluble starches and their derivs., hydroxyalkyl starches, mucopolysaccharides, polyethylene glycol and polypropylene glycol and their copolymers, proteins and their derivs., surfactants polyols, polymethacrylates, polymethyl acrylates, liposomes and emulsified fats.

(III) is selected from sugar phosphates, inositol phosphates, inositol sulphates, nucleotide phosphates, pyridoxal phosphates or sulphates, mucopolysacchardies, 2-naphthol phosphates, salicyclic acid, p-hydroxybenzoic acid, aromatic aldehydes, benzenesulphonic acids and their derivs.

USE/ADVANTAGE - (I) are useful as blood substitutes or extenders. They have a better O2 affinity than crosslinked haemoglobins, a longer intravascular residence **time** than stroma-free **haemoglobin**, and good osmotic, rheological and **stability** properties.

0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: A12-V02; B03-D; B04-B01B; B04-B03; B04-B04A; B04-B04D; B04-C02; B04-C03; B05-B01M; B05-B01N; B05-B01P; B10-A09A; B10-A09B; B10-C03; B10-D01; B12-H06

ABEQ US 4698387 A UPAB: 19930925

An allosterically active conjugate compsn. of **haemoglobin** (I) comprises at least one **tetramer** of **haemoglobin**, and at least one adduct (II) of a **polymer** covalently linked to at least one ligand, so that (II) is reversibly and non-covalently bound to the allosteric binding site of the haemoglobin, and the ligand contains no grps. reactive with it.

USE/ADVANTAGE - (I) is a blood substitute (II) is physiologically acceptable and non toxic.

L122 ANSWER 51 OF 77 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1984-288174 [46] WPIX
DOC. NO. CPI: C1984-122491
TITLE: **Stable tetrameric haemoglobin** crosslinked prods. - useful as oxygen transporting media especially for emergency use.
DERWENT CLASS: B04
PATENT ASSIGNEE(S): (TYER-I) TYE R W
COUNTRY COUNT: 33
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

```
WO 8404248      A  19841108 (198446)* EN   30          <--
   RW: AT BE CF CG CH CM DE FR GA GB LU MR NL SE SN TD TG
    W: AU BR DK FI HU JP KP LK MC MG MW NO RO SU
AU 8429652      A  19841119 (198506)                    <--
EP 143832       A  19850612 (198524)  EN                <--
    R: AT BE CH DE FR GB LI LU NL SE
US 4529719      A  19850716 (198531)                    <--
EP 143832       B  19890215 (198907)  EN                <--
    R: AT BE CH DE FR GB LI LU NL SE
DE 3476735      G  19890323 (198913)                    <--
```

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 8404248	A	WO 1984-US696	19840504	<--
EP 143832	A	EP 1984-902156	19840504	<--
US 4529719	A	US 1983-497454	19830504	<--

PRIORITY APPLN. INFO: **US 1983-497454**
19830504
REFERENCE PATENTS: 8.Jnl.Ref; EP 78961; FR 2288528; FR 2302104; US 4001401; US 4053590; US 4061736; US 4136093
INT. PATENT CLASSIF.: A23J001-06; A61K035-14; A61K037-00; C07C069-00; C07D211-72; C07D213-78; C07G007-00; C07K015-22

BASIC ABSTRACT:

WO 8404248 A UPAB: 19930925
Stroma free **tetrameric** mammalian **haemoglobin** covalently cross-linked with a diamide-forming moiety derived from a bis-diaspirin ester (I) and covalently modified with pyridoxal 5'-phosphate (II). The (II) covalent modifying bond is reduced. The cross-linking and modifying covalent bonds occur in the beta cleft.

The haemoglobin prods. are suitable as oxygen-transporting media, as they have significant intravascular retention and adequate oxygen transport capability. The prods. are superior in use, as in emergency situations, type and crossmatch before transfusion are unnecessary. They have a storage life over 2 years. They are superior to perfluorochemicals because delivery of adequate vols. of O2 found in room air at 1 atmos. pressure rather than 75% O2 is possible also sensitivity problems are avoided. Rapid treatment of hypovolaemic shock is possible, but the prods. ate ideal substitutes for whole blood used to prime the extracorporeal pumps used in cardiac by-pass surgery, as cadaver organ perfusate etc.
0/3

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B04-B03D; B12-H06

ABEQ EP 143832 B UPAB: 19930925
Stroma-free **tetrameric** mammalian **hemoglobin** covalently crosslinked with a diamide bond-forming moiety having the structure (I) wherein R has a chain length of 1,2,3 or 4 units selected from -CH= and -CH2-, said diamide bond-forming moiety being derived from a bis-diaspirin ester, the diaspirin moiety having the structure (II) wherein X1 and X2 are selected from -H, -Br, -I, and -NO2 and wherein either X1 or X2 or both are present said stroma-free **tetrameric hemoglobin** additionally being covalently bound to pyridoxal-5'-phosphate, wherein said pyridoxal-5'-phosphate covalent bond is reduced, and wherein said crosslinking and covalent bonds occur in the beta cleft.

ABEQ US 4529719 A UPAB: 19930925
O2 transporting stroma free tense state **tetrameric** mammalian

haemoglobin crosslinked with a diamide bond forming moiety is derived from (a) a bis-diaspirin ester and is covalently modified with (b) a pyridoxal-5'-phosphate, whose covalent modifying bond is reduced. The crosslinking and modifying covalent bond occur in the beta cleft.

Human, bovine, ovine or porcine haemoglobin can be used. The bis-diaspirin is bis(3,5-di- bromosalicyl)-fumarate or succinate. The beta cleft crosslinking occurs between the alpha-amino of beta1Val1 and the epsilon amino of beta2Lys82. The product is esp. obtd. by (A) allowing stroma free **tetrameric haemoglobin** in the tense state to react covalently with a bis-diaspirin and then the pyridoxal-5'-phosphate and (B) reducing the covalent bond of the reversible Schiff base. The diamide bond forming moiety has the structure -C(O)-R-C(O)-, where R is a chain of 1-4 -CH- or -CH2- units. The diaspiron moiety has structure (I), where each X is independently H, Br, I or NO2.

USE/ADVANTAGE - As resuscitation fluid; a stable O2 carrying protein is provided able to deliver O2 to perfused tissue and to advantageously remain in the intravascular space.

=> d ibib ed ab hitind 52-77
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' - CONTINUE? (Y)/N:y

L122 ANSWER 52 OF 77 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001568075 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11673898
TITLE: Mass spectral analysis of asymmetric hemoglobin hybrids: demonstration of Hb FS (alpha2gammabetaS) in sickle cell disease.
AUTHOR: Ofori-Acquah S F; Green B N; Davies S C; Nicolaides K H; Serjeant G R; Layton D M
CORPORATE SOURCE: Department of Haematological Medicine, Guy's, King's, and St Thomas' School of Medicine, Denmark Hill, London, SE5 9RS, United Kingdom.. soforia@usamail.usouthal.edu
SOURCE: Analytical biochemistry, **(2001 Nov 1)** Vol. 298, No. 1, pp. 76-82.
Journal code: 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Oct 2001
Last Updated on STN: 15 Feb 2002
Entered Medline: 14 Feb 2002

ED Entered STN: 25 Oct 2001
Last Updated on STN: 15 Feb 2002
Entered Medline: 14 Feb 2002

AB Formation of the asymmetric **hemoglobin** hybrid FS (alpha2gammabetaS) inhibits **hemoglobin** S (**Hb** S) **polymerization** in vitro and underlies the protective effect of fetal **hemoglobin** (**Hb** F) in homozygous sickle cell disease. Conventional methods for separating **Hb** reveal only symmetric **Hb tetramers** because of the rapid dissociation of **tetramers** to dimers relative to the separation **time** for electrophoresis and chromatography. To gain insight into the quantitative distribution of asymmetric **Hb** FS and other

tetrameric species in sickle cell disease, the noncovalent association of **Hb** subunits in hemolysates was studied by a novel application of electrospray ionization mass spectrometry (ESI-MS). Mass spectra of both patient and fetal blood revealed predominance of **tetrameric** species with dimer and monomer subunits in lower abundance. ESI-MS analysis revealed the hybrid Hb AF (alpha2gammabetaA) in hemolysates shown by conventional high-performance liquid chromatography to contain only the symmetric species Hb A (alpha2betaA2) and Hb F (alpha2gamma2). A unique **tetramer** of average mass 64,558 Da was identified in hemolysates from patients with sickle cell disease in accordance with the calculated mass of the asymmetric Hb hybrid FS. Hybrid **Hb** species were **stable** under the ESI-MS conditions employed allowing concurrent determination of the proportions of **Hb** FS and the symmetrical Hb S (alpha2betaS2). The ratios of Hb FS to Hb S correlated closely (r2 = 0.96) with those predicted under physiological conditions.

CT Check Tags: Female; Male
Adolescent
Adult
*Anemia, Sickle Cell: BL, blood
Child
Child, Preschool
Chromatography, High Pressure Liquid: MT, methods
*Fetal Blood: CH, chemistry
***Fetal Hemoglobin: AN, analysis**
Hemoglobin A: AN, analysis
***Hemoglobin, Sickle: AN, analysis**
***Hemoglobins: AN, analysis**
Humans
Infant
Middle Aged
Research Support, Non-U.S. Gov't
*Spectrometry, Mass, Electrospray Ionization: MT, methods

RN 9034-51-9 (Hemoglobin A); 9034-63-3 (Fetal Hemoglobin)

CN 0 (Hb FS hemoglobin); 0 (Hemoglobin, Sickle); 0 (Hemoglobins)

L122 ANSWER 53 OF 77 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2001434656 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11307949

TITLE: Expression and properties of recombinant HbA2 (alpha2delta2) and hybrids containing delta-beta sequences.

AUTHOR: Inagaki K; Inagaki J; Dumoulin A; Padovan J C; Chait B T; Popowicz A; Manning L R; Manning J M

CORPORATE SOURCE: Okayama University, Japan.

SOURCE: Journal of protein chemistry, **(2000 Nov)** Vol. 19, No. 8, pp. 649-62.
Journal code: 8217321. ISSN: 0277-8033.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108

ENTRY DATE: Entered STN: 6 Aug 2001
Last Updated on STN: 6 Aug 2001
Entered Medline: 2 Aug 2001

ED Entered STN: 6 Aug 2001
Last Updated on STN: 6 Aug 2001
Entered Medline: 2 Aug 2001

AB Hemoglobin A2 (alpha2delta2), which is present at low concentration (1-2%)

in the circulating red cells of normal individuals, has two important features that merit its study, i.e., it inhibits **polymerization** of sickle **HbS** and its elevated concentration in some thalassemias is a useful clinical diagnostic. However, reports on its functional properties regarding O2 binding are conflicting. We have attempted to resolve these discrepancies by expressing, for the first **time**, recombinant **hemoglobin** A2 and systematically studying its functional properties. The construct expressing HbA2 contains only alpha and delta genes so that the extensive purification required to isolate natural HbA2 is circumvented. Although natural hemoglobin A2 is expressed at low levels in vivo, the amount of recombinant alpha2delta2 expressed in yeast is similar to that found for adult hemoglobin A and for fetal hemoglobin F when the alpha + beta or the alpha + gamma genes, respectively, are present on the construct. Recombinant HbA2 is **stable**, i.e., not easily oxidized, and it is a cooperative functional **hemoglobin** with **tetramer** -dimer dissociation properties like those of adult HbA. However, its intrinsic oxygen affinity and response to the allosteric regulators chloride and 2,3-diphosphoglycerate are lower than the corresponding properties for adult hemoglobin. Molecular modeling studies which attempt to understand these properties of HbA2 are described.

CT Amino Acid Sequence
Biopolymers
Hemoglobin A2: CH, chemistry
Hemoglobin A2: GE, genetics
***Hemoglobin A2: ME, metabolism**
Molecular Sequence Data
Oxygen: ME, metabolism
Protein Conformation
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
Saccharomyces cerevisiae: ME, metabolism
Spectrum Analysis
RN 7782-44-7 (Oxygen); 9034-53-1 (Hemoglobin A2)
CN 0 (**Biopolymers**); 0 (Recombinant Proteins)

L122 ANSWER 54 OF 77 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 96190082 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8608256
TITLE: **Polymerization** of recombinant **hemoglobin** F gamma E6V and **hemoglobin** F gamma Q87T alone, and in mixtures with hemoglobin S.
AUTHOR: Adachi K; Pang J; Konitzer P; Surrey S
CORPORATE SOURCE: Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
CONTRACT NUMBER: HL38632 (NHLBI)
SOURCE: Blood, **(1996 Feb 15)** Vol. 87, No. 4, pp. 1617-24. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 5 Jun 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 29 May 1996

ED Entered STN: 5 Jun 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 29 May 1996

AB To further understand determinants for **Hemoglobin** (**Hb**) S **polymerization**, as well as the inhibitory mechanism of **Hb** F on **Hb** S **polymerization**, **Hb** F variants containing Val-gamma 6 (**Hb** F gamma E6V) or Val-gamma 6, Thr-gamma 87 (Hb F gamma E6V, gamma Q87T) were expressed in yeast. The oxy form of **Hb** F gamma E6V was about 10-fold less **stable** to mechanical agitation than native oxy **Hb** F, which is similar to **stability** differences comparing oxy **Hb** S and oxy **Hb** A. Deoxy Hb F gamma E6V showed approximately 20-fold decreased solubility compared with native deoxy Hb F in high phosphate buffer and formed gels like deoxy Hb S in low phosphate buffer, indicating that the Val-gamma 6 substitution decreases solubility of Hb F like Val-beta 6 in deoxy Hb S. Oversaturated deoxy **Hb** F gamma E6V **polymerized** without a delay **time** in low and high phosphate buffers, in contrast to deoxy **Hb** S, which is accompanied by a distinct delay **time** before **polymerization**. Deoxy **Hb** F gamma E6V, gamma Q87T also **polymerized** without a delay **time** like deoxy **Hb** F gamma E6V. These results suggest that deoxy **Hb** F gamma E6V gamma Q87T **polymers** are different from those of deoxy **Hb** S, and that contact sites differ from those of deoxy Hb S, even though both have the same primary donor (A3) and acceptor sites in the EF helix. These results also suggest that other amino acids in addition to beta 6 Val and amino acids in the F helix are critical for nucleation-controlled **polymerization** of deoxy **Hb** S. 1:1 mixtures of deoxy **Hb** S and either **Hb** F variant **polymerized** with a delay **time** when the concentrations for the **Hb** S/ **Hb** F gamma E6V and **Hb** S/**Hb** F gamma E6V, gamma Q87T mixtures were about 2- and 1.5-fold, respectively, higher than that for Hb S. Logarithmic plots of delay **time** versus concentration for **Hb** S/**Hb** F gamma E6V mixtures showed the same straight line as the line for Hb S/Hb S beta T87Q mixtures, but values for Hb S/Hb F gamma E6V, gamma Q87T mixtures were intermediate between those for Hb S and Hb S/Hb F gamma E6V mixtures. A 1:1 mixture of deoxy **Hb** A and **Hb** F gamma E6V, gamma Q87T also **polymerized**, but exhibited biphasic kinetics, when the concentration was increased to more than 3.5-fold higher than that required for **Hb** S **polymer** formation. These results suggest that Gin-gamma 87 is a critical amino acid for exclusion of FS hybrids (alpha 2 beta S gamma) from nuclei formation with Hb S. Our findings also show that Val-gamma 6 in hybrids that form in mixtures of the Hb F variants with either Hb S or Hb A interacts with the hydrophobic acceptor pocket on the EF helix of an adjacent **tetramer** containing Thr-beta 87.

CT Base Sequence
DNA Primers: CH, chemistry
***Fetal Hemoglobin: CH, chemistry**
***Hemoglobin, Sickle: CH, chemistry**
Humans
Kinetics
Molecular Sequence Data
Point Mutation
Polymers
Protein Binding
Recombinant Proteins
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Solubility
Structure-Activity Relationship

RN 9034-63-3 (Fetal Hemoglobin)

CN 0 (DNA Primers); 0 (Hemoglobin, Sickle); 0 (**Polymers**); 0 (Recombinant Proteins)

L122 ANSWER 55 OF 77 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 95081097 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7989324
TITLE: Role of hydrophobicity of phenylalanine beta 85 and leucine beta 88 in the acceptor pocket for valine beta 6 during **hemoglobin** S **polymerization.**
AUTHOR: Adachi K; Reddy L R; Surrey S
CORPORATE SOURCE: Division of Hematology, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Pennsylvania 19104.
CONTRACT NUMBER: HL-32908 (NHLBI)
P60 HL-38632 (NHLBI)
SOURCE: The Journal of biological chemistry, **(1994 Dec 16)** Vol. 269, No. 50, pp. 31563-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 24 Jan 1995
Last Updated on STN: 24 Jan 1995
Entered Medline: 12 Jan 1995

ED Entered STN: 24 Jan 1995
Last Updated on STN: 24 Jan 1995
Entered Medline: 12 Jan 1995

AB Characterization of the hydrophobic EF acceptor pocket involving Phe-beta 85 and Leu-beta 88 as well as the Val-beta 6 donor site is critical for understanding the **polymerization** of deoxy **Hb** S. Glu substitutions at beta 85 or beta 88 in Hb S were made and expressed in yeast in an effort to evaluate the role of hydrophobicity in the acceptor pocket during **polymerization** of **Hb** S. Both substitutions result in decreased **tetramer stability**, increases in oxygen affinity, and inhibition in **polymerization** compared with **Hb** S. Critical concentrations for **polymerization** of **Hb** SF beta 85E and **Hb** SL beta 88E were 2.4- and 7-fold higher, respectively, than that of Hb S, while the value for Hb SL beta 88E was intermediate between those previously reported for Hb SL beta 88A and Hb SL beta 88F (Adachi, K., Konitzer, P., Paulraj, C. G., and Surrey, S. (1994) J. Biol. Chemical 269, 17477-17480). Kinetics of **polymerization** of Glu-beta 85 and Glu-beta 88 deoxy **Hb** S **tetramers** were biphasic at lower **hemoglobin** concentrations like deoxy **Hb** SL beta 88A, suggesting formation of two types of **polymers** during **polymerization.** The **time** required to form half the total amount of **polymer** (t1/2) for deoxy **Hb** SF beta 85E was 10-fold shorter than that for deoxy Hb SL beta 88E. In addition, t1/2 for deoxy Hb SF beta 85E was 2.5-fold shorter, while that for Hb SL beta 88E was 4-fold longer than deoxy Hb SL beta 88A at equivalent concentrations. These results suggest that hydrophobicity of the amino acid at beta 88 appears more critical than that at beta 85 in the acceptor pocket for Val-beta 6. Furthermore, stereospecificity of the acceptor pocket in addition to hydrophobicity of beta 88 are critical for **stable** hydrophobic interactions with Val-beta 6 during deoxy **Hb** S **polymerization.**

CT ***Globins: CH, chemistry**
Heat

***Hemoglobin, Sickle: CH, chemistry**
Humans
In Vitro
Leucine: CH, chemistry
Mutagenesis, Site-Directed
Phenylalanine: CH, chemistry
Polymers
Protein Binding
Protein Denaturation
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Solubility
Structure-Activity Relationship
Valine: CH, chemistry
Water
RN 61-90-5 (Leucine); 63-91-2 (Phenylalanine); 7004-03-7 (Valine); 7732-18-5 (Water); 9004-22-2 (Globins)
CN 0 (Hemoglobin, Sickle); 0 (**Polymers**)

L122 ANSWER 56 OF 77 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 94292503 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8021253
TITLE: Role of Leu-beta 88 in the hydrophobic acceptor pocket for Val-beta 6 during **hemoglobin** S **polymerization.**
AUTHOR: Adachi K; Konitzer P; Paulraj C G; Surrey S
CORPORATE SOURCE: Children's Hospital of Philadelphia, Division of Hematology, University of Pennsylvania School of Medicine 19104.
CONTRACT NUMBER: HL32908 (NHLBI)
HL38632 (NHLBI)
SOURCE: The Journal of biological chemistry, **(1994 Jul 1)** Vol. 269, No. 26, pp. 17477-80.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 15 Aug 1994
Last Updated on STN: 15 Aug 1994
Entered Medline: 29 Jul 1994
ED Entered STN: 15 Aug 1994
Last Updated on STN: 15 Aug 1994
Entered Medline: 29 Jul 1994
AB X-ray crystallographic studies indicate that the hydrophobic acceptor pocket made by E and F helices involving Leu-beta 88 and Phe-beta 85 is critical for the formation of **stable** hydrophobic interactions with Val-beta 6 on an adjacent deoxy-**hemoglobin** (**Hb**) S **tetramer.** Ala and Phe substitutions at the beta 88 position in Hb S were made using a yeast expression system in an effort to clarify the role of Leu-beta 88 in creating a suitable acceptor site for Val-beta 6 during **polymerization** of **Hb** S. Both Ala- and Phe-beta 88 substitutions in **Hb** S inhibited **polymerization** compared with **Hb** S. Critical concentrations for **polymerization** of alpha 2 beta 2 Val-6,Ala-88 and alpha 2 beta 2Val-6,Phe-88 were 6- and 10-fold higher, respectively, than that of Hb S (alpha 2 beta 2Val-6,Leu-88). Deoxy-**Hb** S containing Phe-beta 88 **polymerized** without a delay **time** like Trp-beta 6- and Phe-beta 6-substituted **hemoglobins** (Adachi, K., Konitzer, P.,

Kim, J., Welch, N., and Surrey, S. (1993) J. Biol. Chemical 268, 21650-21656). In contrast, oversaturated deoxy-**Hb** S containing Ala-beta 88 also **polymerized** without a delay **time**; however, with decreasing **hemoglobin** concentrations, the kinetics of **polymerization** were biphasic. At lower **hemoglobin** concentrations, closer to the critical concentration for **polymerization**, deoxy-**Hb** S containing Ala-beta 88 **polymerized** after a distinct delay **time**. These results suggest that bulky beta 88 hydrophobic replacements like Phe may sterically inhibit insertion of Val-beta 6 into the acceptor pocket. In contrast, smaller sized, less hydrophobic amino acids like Ala compared with Leu-beta 88 may allow insertion of Val-beta 6 into the acceptor pocket but may not promote **stable** protein-protein interactions with an adjacent **Hb** molecule. Stereospecificity and hydrophobicity of the Val-beta 6 hydrophobic acceptor pocket as well as the beta 6 amino acid are, therefore, critical for **polymerization** of deoxy-**Hb** S.

CT **Biopolymers**
Heat
***Hemoglobin, Sickle: CH, chemistry**
Hemoglobin, Sickle: GE, genetics
Humans
*Leucine: CH, chemistry
Mutation
Oxygen: CH, chemistry
Recombinant Proteins: CH, chemistry
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
*Valine: CH, chemistry
RN 61-90-5 (Leucine); 7004-03-7 (Valine); 7782-44-7 (Oxygen)
CN 0 (**Biopolymers**); 0 (Hemoglobin, Sickle); 0 (Recombinant Proteins)

L122 ANSWER 57 OF 77 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 94012744 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8408017
TITLE: Effects of beta 6 aromatic amino acids on **polymerization** and solubility of recombinant **hemoglobins** made in yeast.
AUTHOR: Adachi K; Konitzer P; Kim J; Welch N; Surrey S
CORPORATE SOURCE: Children's Hospital of Philadelphia, Department of Pediatrics, Pennsylvania 19104.
CONTRACT NUMBER: HL 32908 (NHLBI)
P60 HL 38632 (NHLBI)
SOURCE: The Journal of biological chemistry, **(1993 Oct 15)** Vol. 268, No. 29, pp. 21650-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Nov 1993

ED Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Nov 1993

AB Valine, leucine, tryptophan, and phenylalanine substitutions at the beta 6 position of hemoglobin (**Hb**) were made using a yeast expression

system coupled with a **polymerase** chain reaction-based mutagenesis strategy. The oxygen affinity and absorption spectra of these mutants were similar to recombinant Hb A except for Hb beta E6W which had a higher absorbance at approximately 280 nm. The deoxy forms of **Hb** beta E6L and **Hb** S showed characteristic delay **times** prior to **polymerization. Tetrameric** deoxy-**Hbs** containing tryptophan or phenylalanine at the beta 6 position had higher solubilities and **polymerized** less readily compared with deoxy-**Hb** S. However, when oversaturated, these **Hbs polymerized** without a delay **time.** These results suggest that **Hb** beta E6W and **Hb** beta E6F form **polymers** upon deoxygenation by a linear **polymerization** mechanism without nuclei formation. During **polymerization,** bulky hydrophobic amino acids, like phenylalanine and tryptophan at the beta 6 position, might interact with the acceptor pocket on the surface of an adjacent **Hb** molecule but may not be able to form **stable** hydrophobic interactions like beta 6 valine and leucine. Difficulty in insertion of the bulky side chains of these aromatic amino acids into the hydrophobic acceptor pocket on an adjacent **tetramer** may inhibit nuclei formation prior to **polymerization.**

CT *Amino Acids: CH, chemistry
Electrophoresis, Cellulose Acetate
***Hemoglobins: CH, chemistry**
Hemoglobins: GE, genetics
Hemoglobins: IP, isolation & purification
Kinetics
Mutagenesis
Polymers
Recombinant Proteins: CH, chemistry
Recombinant Proteins: GE, genetics
Recombinant Proteins: IP, isolation & purification
Research Support, U.S. Gov't, P.H.S.
*Saccharomyces cerevisiae
Solubility
Spectrometry, Fluorescence

CN 0 (Amino Acids); 0 (Hemoglobins); 0 (**Polymers**); 0 (Recombinant Proteins)

L122 ANSWER 58 OF 77 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 94042222 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8226094
TITLE: Hb Shelby [beta 131(H9)Gln-->Lys] in association with **Hb** S [beta 6(A3)Glu-->Val]: characterization, **stability**, and effects on **Hb** S **polymerization.**
AUTHOR: Adachi K; Surrey S; Tamary H; Kim J; Eck H S; Rappaport E; Ohene-Frempong K
CORPORATE SOURCE: Division of Hematology, Children's Hospital of Philadelphia, PA.
CONTRACT NUMBER: HL 32908 (NHLBI)
P60 HL 38632 (NHLBI)
SOURCE: Hemoglobin, **(1993 Aug)** Vol. 17, No. 4, pp. 329-43.
Journal code: 7705865. ISSN: 0363-0269.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312

ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 1 Dec 1993

ED Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 1 Dec 1993

AB When first tested for abnormal hemoglobins, a 2-year-old boy, appeared to have Hb F, Hb S and Hb A2. Confirmatory testing revealed a beta chain variant inherited from his father and beta S from his mother. Analysis of tryptic peptides in conjunction with automated DNA sequence analysis showed that the variant hemoglobin was Hb Shelby [beta 131(H9)Gln-->Lys (CAG-->AAG)]. **Heat** and mechanical **stabilities** of various liganded **Hb** Shelby **tetramers** were compared to those of **Hb** A and **Hb** S. Oxy-**Hb** Shelby precipitated more readily than oxy-**Hb** A, but was much more **stable** than oxy-**Hb** S during mechanical agitation. In contrast, oxy-**Hb** Shelby was much less **stable** than oxy-**Hb** A and oxy-**Hb** S following **heat** treatment. Met-Hb Shelby was most unstable compared to other liganded forms of **Hb** Shelby, while deoxy- and carbonmonoxy-forms of **Hb** Shelby showed similar **heat**-induced precipitation rates. These data indicate that **heat** instability of **Hb** Shelby is accompanied by heme oxidation, and that denaturation by mechanical agitation occurs in the absence of heme oxidation. Hb Shelby, like **Hb** A, can form hybrids with **Hb** S which participate in **polymer** formation in vitro. However, **Hb** S/**Hb** Shelby hybrids **copolymerized** with **Hb** S less than A/S hybrids. Since the patient's MCHC value is normal, this finding coupled with the elevated Hb A2 and **Hb** F levels, both of which are known to inhibit **polymerization** of **Hb** S, may contribute to the patient's mild clinical presentation.

CT Check Tags: Female; Male
Base Sequence
Child, Preschool
***Globins: GE, genetics**
Heat
Hemoglobin, Sickle: CH, chemistry
***Hemoglobins, Abnormal: GE, genetics**
Heterozygote
Humans
Ligands
Molecular Sequence Data
Polymers
Protein Denaturation
Research Support, U.S. Gov't, P.H.S.
*Sickle Cell Trait: GE, genetics
Solubility
Stress, Mechanical

RN 56690-69-8 (hemoglobin Shelby); 9004-22-2 (Globins)

CN 0 (Hemoglobin, Sickle); 0 (Hemoglobins, Abnormal); 0 (Ligands); 0 (**Polymers**)

L122 ANSWER 59 OF 77 MEDLINE on STN
ACCESSION NUMBER: 97059148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8900178
TITLE: Expression studies of delta-globin gene alleles associated with reduced hemoglobin A2 levels in Greek Cypriots.
AUTHOR: Trifillis P; Adachi K; Yamaguchi T; Schwartz E; Surrey S
CORPORATE SOURCE: Division of Hematology, Abramson Pediatric Research Center, The Children's Hospital of Philadelphia, Philadelphia,

Pennsylvania 19104, USA.
CONTRACT NUMBER: DK 16691 (NIDDK)
HL 38632 (NHLBI)
SOURCE: The Journal of biological chemistry, **(1996 Oct 25)**
Vol. 271, No. 43, pp. 26931-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 16 Dec 1996
ED Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 16 Dec 1996

AB We previously identified five delta-globin gene alleles associated with reduced hemoglobin (Hb) A2 (Trifillis, P., Ioannou, P., Schwartz, E., and Surrey, S. (1991) Blood 78, 3298-3305). We have now evaluated functional consequences of the changes after expression in COS-1 cells to monitor effects on RNA splicing. In addition, variant **Hb** A2 **tetramers** were expressed in yeast to assess effects of amino acid changes on oxygen binding and **stability** to heat and mechanical agitation. The G --> T change at codon 27 and the A --> G change in IVS-2 both affect RNA splicing, whereas the C --> T change at codon 97 and the AT deletion in IVS-2 have no effect. Oxygen equilibrium curves of the Hb A2 variants expressed in yeast were similar to that of wild type Hb A2. None of the three variant **Hb** A2 **tetramers** (Thr --> Ile at codon 4 (**Hb** deltaT4I), Ala --> Ser at codon 27 (**Hb** deltaA27S), and Arg --> Cys at codon 116 (**Hb** deltaR116C)) showed decreased **heat stability** compared with **Hb** A2, whereas the **Hb** deltaT4I variant showed highest instability to mechanical agitation. Co-expression in yeast of alpha-globin chain and the delta-chain variant containing a Leu --> Pro change at codon 141 yielded no identifiable **tetramers**, suggesting lack of assembly or severe **tetramer** instability. These studies show the probable cause for decreased **Hb** A2 for two alleles is due to defective splicing, whereas decreased protein **stability**, increased **tetramer** association with red cell membranes, increased interdisulfide bond formation of delta-chains, which inhibits assembly with alpha-chains, and/or reduced assembly is suggested for the other three alleles.

CT *Alleles
Animals
Biopolymers
COS Cells
Cyprus
Genetics, Population
Globins: CH, chemistry
***Globins: GE, genetics**
***Hemoglobin A2: ME, metabolism**
Humans
Mutagenesis, Site-Directed
Mutation
Protein Conformation
RNA Splicing
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
RN 9004-22-2 (Globins); 9034-53-1 (Hemoglobin A2)

CN 0 (**Biopolymers**)

L122 ANSWER 60 OF 77 MEDLINE on STN
ACCESSION NUMBER: 97059114 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8900144
TITLE: Expression of soluble human beta-globin chains in bacteria and assembly in vitro with alpha-globin chains.
AUTHOR: Yamaguchi T; Pang J; Reddy K S; Witkowska H E; Surrey S; Adachi K
CORPORATE SOURCE: The Children's Hospital of Philadelphia, Division of Hematology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
CONTRACT NUMBER: HL20985 (NHLBI)
HL38632 (NHLBI)
RR06505 (NCRR)
SOURCE: The Journal of biological chemistry, **(1996 Oct 25)** Vol. 271, No. 43, pp. 26677-83.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 16 Dec 1996

ED Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 16 Dec 1996

AB Authentic soluble human beta-globin chains were produced in Escherichia coli using an expression plasmid (pHE2beta) containing full-length cDNAs coding for human beta-globin chain and methionine aminopeptidase. Spectral properties of the purified beta-globin were identical to those of authentic beta-globin. Soluble beta-globin showed low (16 kDa) and high molecular mass (32 kDa) forms that could be separated by gel filtration chromatography. SDS-polyacrylamide gel electrophoresis and electrospray mass spectrometry revealed the 32-kDa species was dimeric beta-globin formed by an intermolecular disulfide bond, while the 16-kDa species was authentic monomeric beta-globin. Monomeric forms of beta-globin, like authentic native beta-globin, formed **tetrameric hemoglobin** (**Hb**) A (alpha2beta2) in vitro upon incubation with alpha-globin, while dimeric forms did not. When beta-globin dimers, however, were converted to monomers by incubation with dithiothreitol, the beta-globin chain monomers assembled with alpha-globin and formed **hemoglobin tetramers.** alpha-Globin was more **thermally** unstable than beta-globin, while assembled **tetramers** promoted higher **stability.** Disulfide-bonded beta-globin dimers showed a slight increase in **thermal stability** compared with beta-globin; however, dimers were still more unstable than **tetrameric Hb** A. These results indicate that presence of alpha chains favors assembly with beta-globin, beta-beta dimers cannot bind alpha chains, and that **Hb** A **tetramer** formation results in the most **thermally stable** species.

CT **Biopolymers**
Cloning, Molecular
Escherichia coli: GE, genetics
Globins: CH, chemistry
***Globins: GE, genetics**
Heat

Humans
Isomerism
Peptide Mapping
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Trypsin
RN 9004-22-2 (Globins)
CN 0 (**Biopolymers**); EC 3.4.21.4 (Trypsin)

L122 ANSWER 61 OF 77 MEDLINE on STN
ACCESSION NUMBER: 78006986 MEDLINE
DOCUMENT NUMBER: PubMed ID: 20481
TITLE: Some properties of Hb G San Jose (beta7 glu replaced by gly): comparisons with Hb S.
AUTHOR: Roth E F Jr; Schiliro G; Elbaum D; Musumeci S; Pizzarelli G; Russo G; Nagel R L
SOURCE: The Journal of laboratory and clinical medicine, **(1977 Nov)** Vol. 90, No. 5, pp. 837-43.
Journal code: 0375375. ISSN: 0022-2143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197711
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 30 Nov 1977
ED Entered STN: 14 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 30 Nov 1977
AB Hb G San Jose (beta7 glu leads to gly) was studied with respect to oxygen affinity, Bohr effect, surface activity in dilute aqueous solutions, mechanical precipitability, **heat stability** and its ability to **copolymerize** in the deoxy form with **Hb** S. Oxygen affinity, Bohr effect, and **polymerization** with **Hb** S were found to be identical to those of Hb A when studied under the same conditions. However, surface activity and mechanical precipitation rates of the oxyconformers closely resembled those of oxyhemoglobin S. **Hb** G San Jose was also found to be slightly more unstable with **heat** than **Hb** A, although the instability was not detected by the usual incubation method of 1 hr at 50 degrees and higher temperatures were needed to elicit this difference. It is concluded that the ability to **polymerize** and the presence of increased surface activity are distinct and separable attributes of hemoglobin mutants. The finding that mixtures of Hb S and Hb G San Jose gel like mixtures of Hb S and Hb A supports the conclusion that only one beta 6 Val combining site per **tetramer** is required for **polymer** formation.
CT Check Tags: Male
Adult
Comparative Study
Gels
Heat
***Hemoglobin, Sickle: ME, metabolism**
***Hemoglobins, Abnormal: ME, metabolism**
Humans
Hydrogen-Ion Concentration
In Vitro
Oxygen: BL, blood
Precipitation
Research Support, U.S. Gov't, P.H.S.

Structure-Activity Relationship
Surface Tension
RN 7782-44-7 (Oxygen)
CN 0 (Gels); 0 (Hemoglobin, Sickle); 0 (Hemoglobins, Abnormal)

L122 ANSWER 62 OF 77 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 6

ACCESSION NUMBER: 2001324418 EMBASE
TITLE: **Oligomerization** and ligand binding in a **homotetrameric hemoglobin**: Two high-resolution crystal structures of **hemoglobin** Bart's (γ(4)), a marker for α-thalassemia.
AUTHOR: Kidd R.D.; Baker H.M.; Mathews A.J.; Brittain T.; Baker E.N.
CORPORATE SOURCE: E.N. Baker, School of Biological Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. ted.baker@auckland.ac.nz
SOURCE: Protein Science, (2001) Vol. 10, No. 9, pp. 1739-1749. .
Refs: 56
ISSN: 0961-8368 CODEN: PRCIEI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Oct 2001
Last Updated on STN: 4 Oct 2001

ED Entered STN: 4 Oct 2001
Last Updated on STN: 4 Oct 2001

AB Hemoglobin (Hb) Bart's is present in the red blood cells of millions of people worldwide who suffer from α-thalassemia, α-Thalassemia is a disease in which there is a deletion of one or more of the four α-chain genes, and excess γ and β chains spontaneously form homotetramers. The γ(4) **homotetrameric** protein known as **Hb** Bart's is a **stable** species that exhibits neither a Bohr effect nor heme-heme cooperativity. Although Hb Bart's has a higher O(2) affinity than either adult (α(2)β(2)) or fetal (α(2)γ(2)) Hbs, it has a lower affinity for O(2) than HbH (β(4)). To better understand the association and ligand binding properties of the γ(4) **tetramer**, we have solved the structure of **Hb** Bart's in two different oxidation and ligation states. The crystal structure of ferrous carbonmonoxy (CO) Hb Bart's was determined by molecular replacement and refined at 1.7 A resolution (R = 21.1%, R(free) = 24.4%), and that of ferric azide (N(3)(-)) Hb Bart's was similarly determined at 1.86 A resolution (R = 18.4%, R(free) = 22.0%). In the carbonmonoxy-Hb structure, the CO ligand is bound at an angle of 140°, and with an unusually long Fe-C bond of 2.25 A. This geometry is attributed to repulsion from the distal His63 at the low pH of crystallization (4.5). In contrast, azide is bound to the oxidized heme iron in the methemoglobin crystals at an angle of 112°, in a perfect orientation to accept a hydrogen bond from His63. Compared to the three known quaternary structures of human Hb (T, R, and R2), both structures most closely resemble the R state. Comparisons with the structures of adult **Hb** and HbH explain the association and dissociation behaviour of **Hb homotetramers** relative to the **heterotetrameric Hbs.**

CT Medical Descriptors:
*alpha thalassemia
crystal structure

oligomerization
ligand binding
protein quaternary structure
hydrogen bond
crystallization
stereochemistry
protein tertiary structure
article
priority journal
Drug Descriptors:
***hemoglobin**
ligand
heme
oxygen
hemoglobin F
azide
iron
methemoglobin
hydrogen
histidine
carboxyhemoglobin
carbon monoxide
RN (hemoglobin) 9008-02-0; (heme) 14875-96-8; (oxygen) 7782-44-7; (hemoglobin F) 9034-63-3; (azide) 12596-60-0, 14343-69-2; (iron) 14093-02-8, 53858-86-9, 7439-89-6; (hydrogen) 12385-13-6, 1333-74-0; (histidine) 645-35-2, 7006-35-1, 71-00-1; (carboxyhemoglobin) 9061-29-4; (carbon monoxide) 630-08-0

L122 ANSWER 63 OF 77 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 7
ACCESSION NUMBER: 2001269776 EMBASE
TITLE: Molecular engineering of a **polymer** of **tetrameric hemoglobins.**
AUTHOR: Fronticelli C.; Arosio D.; Bobofchak K.M.; Vasquez G.B.
CORPORATE SOURCE: C. Fronticelli, Johns Hopkins Univ. Sch. of Medicine, Department of Anesthesiology, 600 N. Wolfe St., Baltimore, MD 21287, United States. cfrontic@jhmi.edu
SOURCE: Proteins: Structure, Function and Genetics, (15 Aug 2001) Vol. 44, No. 3, pp. 212-222. .
Refs: 34
ISSN: 0887-3585 CODEN: PSFGEY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2001
Last Updated on STN: 16 Aug 2001
ED Entered STN: 16 Aug 2001
Last Updated on STN: 16 Aug 2001
AB We have engineered a recombinant mutant human **hemoglobin**, **Hb** Prisca β(S9C+C93A+C112G), which assembles in a **polymeric** form. The polymerization is obtained through the formation of intermolecular S-S bonds between cysteine residues introduced at position β9, on the model of Hb Porto Alegre (β9Ser → Cys) (Bonaventura and Riggs, Science 1967;155:800-802). Cβ93 and Cβ112 were replaced in order to prevent formation of spurious S-S bonds during the expression, assembly, and polymerization events. Dynamic light scattering measurements indicate that the final **polymerization** product is mainly formed by 6 to 8

tetrameric hemoglobin molecules. The sample polydispersity Q = 0.07 ± 0.02, is similar to that of purified human hemoglobin (Q = 0.02 ± 0.02), consistent with a good degree of homogeneity. In the presence of strong reducing agents, the polymer reverts to its tetrameric form. During the depolymerization process, a direct correlation is observed between the hydrodynamic radius and the light scattering of the system, which, in turn, is proportional to the mass of the protein. We interpret this to indicate that the **hemoglobin** molecules are tightly packed in the **polymer** with no empty spaces. The tight packing of the **hemoglobin** molecules suggests that the **polymer** has a globular shape and, thus, allows estimation of its radius. An illustration of an arrangement of a finite number of **tetrameric hemoglobin** molecules is presented. The conformational and functional characteristics of this polymer, such as heme pocket conformation, **stability** to denaturation, autoxidation rate, oxygen affinity, and cooperativity, remain similar to those of **tetrameric** human **hemoglobin** . .COPYRGT. 2001 Wiley-Liss, Inc.

CT Medical Descriptors:
*genetic engineering
polymerization
chemical binding
light scattering
depolymerization
hydrodynamics
thermostability
molecular interaction
conformational transition
protein denaturation
oxygen affinity
autooxidation
article
priority journal
Drug Descriptors:
*polymer
*tetramer
***hemoglobin derivative**

L122 ANSWER 64 OF 77 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 79136015 EMBASE
DOCUMENT NUMBER: 1979136015
TITLE: Structural bases of the inhibitory effects of **hemoglobin** F and **hemoglobin** A2 on the **polymerization** of **hemoglobin** S.
AUTHOR: Nagel R.L.; Bookchin R.M.; Johnson J.; et al.
CORPORATE SOURCE: Div. Hematol., Dept. Med., Albert Einstein Coll. Med., Bronx, N.Y. 10461, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1979) Vol. 76, No. 2, pp. 670-672. .
CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
025 Hematology
LANGUAGE: English

AB The inhibitory effect of **hemoglobin** F (**Hb** F) on the **polymerization** of **Hb** S proceeds via the formation of asymmetrical hybrid **tetramers** of the type

α2β(S)γ. Examination of the gelling properties of binary mixtures of Hb S and several Hb variants shows that, among the γ chain amino acid residues that differ from those of the β chain, residues γ80 (EF4) and γ87 (F3) are at least partly responsible for this inhibition. Furthermore, the authors find that mixing Hb A2(α2δ2) with Hb S strongly inhibits gelling to an extent similar to that seen with Hb S/Hb F mixtures; this inhibition is attributable to amino acid differences between the δ and β chain sequences at positions δ22 (B4) and δ87 (F3). Therefore, residues 22, 80 and 87 of the β chain appear to be involved in intermolecular contact sites that **stabilize** the deoxy **Hb** S **polymers.**

CT Medical Descriptors:
human cell
blood and hemopoietic system
Drug Descriptors:
***hemoglobin a2**
***hemoglobin f**
***hemoglobin s**

RN (hemoglobin a2) 37203-64-8, 37203-65-9, 53262-80-9, 9034-53-1, 99493-07-9; (hemoglobin f) 9034-63-3; (hemoglobin s) 9035-22-7

L122 ANSWER 65 OF 77 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 78217588 EMBASE
DOCUMENT NUMBER: 1978217588
TITLE: Some properties of Hb G(San Jose) (β7 glu→gly): Comparisons with Hb S.
AUTHOR: Roth Jr. E.F.; Schiliro G.; Elbaum D.; et al.
CORPORATE SOURCE: Dept. Med., Albert Einstein Coll. Med., Bronx, N.Y. 10461, United States
SOURCE: Journal of Laboratory and Clinical Medicine, (1977) Vol. 90, No. 5, pp. 837-843. .
CODEN: JLCMAK
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

AB Hb G(San Jose) (β7 glu→gly) was studied with respect to oxygen affinity, Bohr effect, surface activity in dilute aqueous solutions, mechanical precipitability, **heat stability** and its ability to **copolymerize** in the deoxy form with **Hb** S. Oxygen affinity, Bohr effect, and **polymerization** with **Hb** S were found to be identical to those of **Hb** A when studied under the same conditions. However, surface activity and mechanical precipitation rates of the oxyconformers closely resembled those of oxyhemoglobin S. Hb G(San Jose) was also found to be slightly more unstable with **heat** than Hb A, although the instability was not detected by the usual incubation method of 1 hr at 50° and higher **temperatures** were needed to elicit this difference. It is concluded that the ability to **polymerize** and the presence of increased surface activity are distinct and separate attributes of **hemoglobin** mutants. The finding that mixtures of Hb S and Hb G(San Jose) gel like mixtures of Hb S and **Hb** A supports the conclusion that only one β6 Val combining site per **tetramer** is required for polymer formation.

CT Medical Descriptors:
*hemoglobin g san jose
theoretical study
in vitro study

Drug Descriptors:
***hemoglobin s**
***hemoglobin variant**
RN (hemoglobin s) 9035-22-7

L122 ANSWER 66 OF 77 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 2
ACCESSION NUMBER: 2003:275285 BIOSIS
DOCUMENT NUMBER: PREV200300275285
TITLE: Water regulates oxygen binding in hagfish (Myxine glutinosa) hemoglobin.
AUTHOR(S): Muller, Gabriele; Fago, Angela [Reprint Author]; Weber, Roy E.
CORPORATE SOURCE: Department of Zoophysiology, Institute of Biology, University of Aarhus, Building 131, DK-8000, Aarhus C, Denmark
angela.fago@biology.au.dk
SOURCE: Journal of Experimental Biology, (**April 2003**) Vol. 206, No. 8, pp. 1389-1395. print.
ISSN: 0022-0949 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003
ED Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003
AB Hagfish hemoglobin (Hb) is considered to represent a transition stage between invertebrate and vertebrate hemoglobins. The Hb system of Myxine glutinosa consists of three monomeric **hemoglobins**, which upon deoxygenation associate to form primarily heterodimers and **heterotetramers.** Myxine glutinosa is an osmoconformer, whose red blood cells show the exceptional ability to swell and remain swollen under hyposmotic conditions. In order to determine whether water activity regulates hemoglobin function, the effect of changes in osmolality on hemoglobin-O2 affinity was investigated by applying the osmotic stress method to purified hemoglobins as well as intact red blood cells. Oxygen affinity decreases when water activity increases, indicating that water molecules **stabilize** the low-affinity, **oligomeric** state of the **hemoglobin.** This effect is opposite to that observed in **tetrameric** vertebrate **hemoglobins**, but resembles that seen in the dimeric **hemoglobin** of the marine clam Scapharca inaequivalvis. Our data show that water may act as an allosteric effector for hemoglobin within intact red cells and even in animals that do not experience large variations in blood osmolality.
CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Porphyrins and bile pigments 10065
Physiology - General 12002
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Chemical Coordination and Homeostasis
IT Parts, Structures, & Systems of Organisms
blood: blood and lymphatics, osmolality
IT Chemicals & Biochemicals
hemoglobin
IT Miscellaneous Descriptors
osmotic stress; oxygen affinity; oxygen binding regulation; water activity; water effect

ORGN Classifier
Agnatha 85201
Super Taxa
Pisces; Vertebrata; Chordata; Animalia
Organism Name
Myxine glutinosa (species) [hagfish (common)]
Taxa Notes
Animals, Chordates, Fish, Nonhuman Vertebrates, Vertebrates

L122 ANSWER 67 OF 77 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:241303 BIOSIS
DOCUMENT NUMBER: PREV200200241303
TITLE: Deoxyhemoglobin S polymers tend to extrude 2,3-DPG into the sol phase.
AUTHOR(S): Bookchin, Robert M. [Reprint author]; Balazs, Tania [Reprint author]
CORPORATE SOURCE: Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 487a-488a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Apr 2002
Last Updated on STN: 17 Apr 2002
ED Entered STN: 17 Apr 2002
Last Updated on STN: 17 Apr 2002
AB Deoxygenation-induced **polymerization** of **hemoglobin** (**Hb**) S in solutions or within sickle cell anemia (SS) RBC generates 2 phases and 3 compartments: the sol phase, containing **unpolymerized Hb**; and the **polymer** phase, made up of the **polymerized Hb tetramers** and the **polymer** water compartment (PWC). The PWC excludes soluble Hb and most non-interactive molecules with MW>1000 kDa, and comprises apprx60% (v/v) of the total polymer phase (J Mol Biol 244:100, 1994). Deoxygenation of dense SS RBC generates relatively large polymer phase fractions, whose PWC may contain 60-80% of the cell water; substantial redistribution of cell solutes which do not fully partition in the PWC could have significant metabolic and functional effects. In this study of the distribution of functionally important RBC solutes between the sol and PWC, including any binding to **polymerized Hb**, we measured the effects of **polymerization** on the.distribution of 2,3-DPG, in near-physiological conditions. Solutions containing 20-25 g/dl Hb S (in 0.05 M bis-tris+0.1 M NaCl) and 0.5 to 2.0 moles DPG per mole **Hb tetramer** (or no DPG) were deoxygenated with 50 mM Na-dithionite, ultracentrifuged, and measurements were made of the Csat's and of the molar ratios of DPG:Hb in the initial mixtures and in the separated sol and pellet phases. The fraction of trapped sol in the pellet was measured with 14C-dextran (70 kDa), which does not enter the PWC. Since DPG is known to bind to deoxyHb almost stoichiometrically, with a KD of apprx2.5X10-5, and has a normal allosteric effect with Hb S, it was surprising to find DPG:Hb consistently decreased in the pellet phase, and increased in the sol phase: With initial DPG:**Hb** apprx1, after deoxygenation, DPG:**Hb** in the **polymer**

phase (the pellet, corrected for apprx10% measured trapped sol) ranged between 0.35 and 0.65, while the DPG:Hb in the sol phase consistently exceeded 1, accounting for the initial total DPG. With initial DPG: **Hb** apprx0.50, the ratio was 0.33 in the **polymer** phase and 0.65 in the sol phase. Measures to exclude artifacts by varying experimental conditions, i.e., deoxygenation without dithionite, variations in the final pH between 6.8 and 7.2, alternate buffer (HEPES), and use of two different methods to quantitate DPG, enzymatic or as inorganic phosphate, had no qualitative effect on the results. In all the experiments, DPG had small, inconsistent effects on the Csat. These results suggest that DPG tends to be excluded from the deoxy-**Hb** S **tetramers** within the **polymer**, and relatively concentrated in the sol phase. The data do not distinguish how much of the DPG in the polymer phase is in the PWC. Its molecular mass (266 kDa) should permit inclusion; the effect of the polyanionic charge is unknown. Given the relatively lowered DPG:**Hb** ratios in the **polymer** phase, if DPG does partition substantially in the PWC, there must be less bound to deoxy-**Hb** S, and its exclusion by the **polymerized Hb** would accordingly be greater. These results are not consistent with a commonly held notion that DPG promotes **polymerization** by **stabilizing** the deoxy conformation of **Hb** S within the **polymer**, and suggest rather that the central cavity DPG-binding region of deoxy-**Hb** S may be perturbed in the **polymer.** The precise role of DPG in the polymerization mechanisms, and its activity in the partitions within sickled RBC, will need further clarification.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004

IT Major Concepts
Blood and Lymphatics (Transport and Circulation)

IT Parts, Structures, & Systems of Organisms
RBC: blood and lymphatics, red blood cell

IT Chemicals & Biochemicals
2,3-DPG: distribution; C-sat; HEPES; [carbon-14]-dextran; deoxyhemoglobin D polymer; hemoglobin S; polymer water compartment; sodium chloride; sodium-dithionite

IT Miscellaneous Descriptors
pellet phase; sol phase; Meeting Abstract; Meeting Poster

RN 138-81-8 (2,3-DPG)
7365-45-9 (HEPES)
7647-14-5 (sodium chloride)
7775-14-6 (sodium-dithionite)

L122 ANSWER 68 OF 77 PASCAL COPYRIGHT 2006 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0059102 PASCAL

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TITLE (IN ENGLISH): A recombinant **polymeric hemoglobin** with conformational, functional, and physiological characteristics of an in vivo O.sub.2 transporter

AUTHOR: BOBOFCHAK Kevin M.; MITO Toshiaki; TEXEL Sarah J.; BELLELLI Andrea; NEMOTO Masaaki; TRAYSTMAN Richard J.; KOEHLER Raymond C.; BRINIGAR William S.; FRONTICELLI Clara

CORPORATE SOURCE: Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, United States; Consiglio

Nazionale della Ricerca, Institute of Molecular Biology and Pathology and Department Biochemical Sciences University La Sapienza, Rome, Italy; Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, United States
SOURCE: American journal of physiology. Heart and circulatory physiology, **(2003)**, 54(2), H549-H561, 53 refs.
ISSN: 0363-6135 CODEN: AJPPDI
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-670D, 354000119988700130
UP 20040217
AB With the objective of developing a recombinant oxygen carrier suitable for therapeutic applications, we have employed an Escherichia coli expression system to synthesize in high-yield **hemoglobin** (**Hb**) Minotaur, containing α-human and β-bovine chains. **Polymerization** of **Hb** Minotaur through S-S intermolecular cross-linking was obtained by introducing a Cys at position β9 and substituting the naturally occurring Cys. This homogeneous **polymer**, **Hb** Polytaur, has a molecular mass of - 500 kDa and was resistant toward reducing agents present in blood. In mice, the circulating half-**time** (3 h) was fivefold greater than adult human Hb (HbA). The half-**time** of autooxidation measured in blood (46 h) exceeded the circulating retention **time.** Hypervolemic exchange transfusion resulted in increased arterial blood pressure similar to that with albumin. The increase in pressure was less than that obtained by transfusion of cross-linked **tetrameric Hb** known to undergo renovascular extravasation. The nitric oxide reactivity of Hb Polytaur was similar to HbA, suggesting that the diminished pressor response to Hb Polytaur was probably related to diminished extravasation. Transfusion of 3% Hb Polytaur during focal cerebral ischemia reduced infarct volume by 22%. Therefore, site-specific Cys insertion on the **Hb** surface results in uniform size **polymers** that do not produce the large pressor response seen with **tetrameric Hb.** **Polymerization** maintains physiologically relevant oxygen and heme affinity, **stability** toward denaturation and oxidation, and effective oxygen delivery as indicated by reduced cerebral ischemic damage.

L122 ANSWER 69 OF 77 BIOENG COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2004311047 BIOENG
DOCUMENT NUMBER: 0230804
TITLES: Acellular resuscitative compounds
AUTHOR: Cerny, Lawrence C; Cerny, Elaine R
CORPORATE SOURCE: Cernyland of Utica, Huber Hts., OH, USA
SOURCE: SOUTH BIOMED ENG CONF PROC, IEEE, PISCATAWAY, NJ, (USA), 1996, pp. 548-551,
Conference: The 1996 15th Southern Biomedical Engineering Conference, Dayton, OH, USA, 03/29-31/96
Published by: IEEE, PISCATAWAY, NJ, (USA)
DOCUMENT TYPE: Book; Conference
LANGUAGE: English
UP 20040602
AB There exists a need for a safe, efficacious emergency blood substitute for human use when whole blood is unavailable. This substitute should provide an acceptable volume expansion as well as tissue oxygenation

delivery without requiring oxygen-enriched mixtures. It would be advantageous if this material could be **stored** at room **temperature** in a dehydrated state for prolonged periods of **time.** During the past several years, it has been possible to achieve these goals using modified hydroxyethyl starches complexed with **stabilized hemoglobins.** In this article, the following will be discussed: 1) The synthesis of a modified hydroxyethyl starch to an aldehyde **polymer**; 2) Two methods to **stabilize** the **tetramers** of **hemoglobin**; 3) The synthesis of **polymer-hemoglobin** resuscitative compounds. The ultimate goal of this investigation is a personalized blood service in which you would donate your own blood, have it converted to an acellular compound, carry it with you in freeze-dried form... ready for use in any emergency just by reconstituting with water.

L122 ANSWER 70 OF 77 BIOENG COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2004275218 BIOENG
DOCUMENT NUMBER: 0152643
TITLES: Starch-hemoglobin resuscitative compound
AUTHOR: Cerny, LC; Barnes, B; Fisher, L; Anibarro, M; Cerny, ER
CORPORATE SOURCE: Utica Coll of Syracuse Univ, Utica, NY, USA
SOURCE: ARTIF CELLS BLOOD SUBSTITUTES IMMOBILIZATION BIOTECHNOL, vol. 22, no. 5, A86, 1994
Conference: The 11th Congress of the International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology, (ISABI), Boston, MA, USA, 07/24-27/94
ISSN: 1073-1199
DOCUMENT TYPE: Journal; Conference
LANGUAGE: English
UP 20040602
AB A resuscitative compound in freeze-dried form has been synthesized between a modified starch and a **tetramerically stabilized hemoglobin.** In order to complex the **hemoglobin**, the starch has been prepared in mono-, di-, tri- and tetra-aldehyde moieties. The **hemoglobin** was **stabilized** with low molecular weight diacids. The resulting **polymers** were characterized with respect to the average molecular weight, second virial coefficient, intrinsic viscosity, oxygen transport, Hill constant, P sub(50) and Bohr effect. The in vitro evaluation indicates that these compounds are effective hemodiluents, offer protection to the red cell membrane and do not cause erythrocyte aggregation.

L122 ANSWER 71 OF 77 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 93:77174 LIFESCI
TITLE: Effects of beta 6 amino acid hydrophobicity on **stability** and solubility of **hemoglobin tetramers.**
AUTHOR: Adachi, K.; Kim, J.Y.; Konitzer, P.; Asakura, T.; Saviola, B.; Surrey, S.
CORPORATE SOURCE: Div. Hematol., Children's Hosp. Philadelphia, 34th St. and Civic Cent. Blvd., Philadelphia, PA 19104, USA
SOURCE: FEBS LETT., **(1993)** vol. 35, no. 1, pp. 47-50.
ISSN: 0014-5793.
DOCUMENT TYPE: Journal
FILE SEGMENT: L
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The relationship between different amino acids at the beta 6 position of **hemoglobin** and **tetramer stability** was

addressed by a site-directed mutagenesis approach. Precipitation rates during mechanical agitation of oxyhemoglobins with Gln, Val, Leu and Trp at the beta 6 position increased 2, 5, 13, 21 and 53 **times**, respectively, compared with that for Hb A. There was a linear relationship between the log of the precipitation rate constant and amino acid hydrophobicity at the beta 6 position, suggesting that enhanced precipitation of oxy Hb S results in part from increased hydrophobicity of beta 6 Val. Deoxyhemoglobin solubility increased in the order of beta 6 Ile, Leu, Val, Trp, Gln, Ala and Glu suggesting that hydrophobic interactions between beta 6 Val and the acceptor site of another **hemoglobin** molecule during deoxy-**Hb** S **polymerization** depend on hydrophobicity and stereospecificity of the amino acid side chain at the beta 6 position. Our results indicate that hydrophobic amino acids at the beta 6 position which promote tetramer instability in the oxy form do not necessarily promote polymerization in the deoxy form.

L122 ANSWER 72 OF 77 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:36885885 BIOTECHNO
TITLE: A recombinant **polymeric hemoglobin** with conformational, functional, and physiological characteristics of an in vivo O.sub.2 transporter
AUTHOR: Bobofchak K.M.; Mito T.; Texel S.J.; Bellelli A.; Nemoto M.; Traystman R.J.; Koehler R.C.; Brinigar W.S.; Fronticelli C.
CORPORATE SOURCE: C. Fronticelli, Dept. Anesth. and Critical Care Med., Johns Hopkins Univ. Sch. of Medicine, 600 N. Wolfe St., Baltimore, MD 21287, United States.
E-mail: cfrontic@jhmi.edu
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, **(01 AUG 2003)**, 285/2 54-2 (H549-H561), 53 reference(s)
CODEN: AJPPDI ISSN: 0363-6135
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ED 20030812
AB With the objective of developing a recombinant oxygen carrier suitable for therapeutic applications, we have employed an Escherichia coli expression system to synthesize in high-yield **hemoglobin** (**Hb**) Minotaur, containing α-human and β-bovine chains. **Polymerization** of **Hb** Minotaur through S-S intermolecular cross-linking was obtained by introducing a Cys at position β9 and substituting the naturally occurring Cys. This homogeneous **polymer**, **Hb** Polytaur, has a molecular mass of .apprx.500 kDa and was resistant toward reducing agents present in blood. In mice, the circulating half-**time** (3 h) was fivefold greater than adult human Hb (HbA). The half-**time** of autooxidation measured in blood (46 h) exceeded the circulating retention **time.** Hypervolemic exchange transfusion resulted in increased arterial blood pressure similar to that with albumin. The increase in pressure was less than that obtained by transfusion of cross-linked **tetrameric Hb** known to undergo renovascular extravasation. The nitric oxide reactivity of Hb Polytaur was similar to HbA, suggesting that the diminished pressor response to Hb Polytaur was probably related to diminished extravasation. Transfusion of 3% Hb Polytaur during focal cerebral ischemia reduced infarct volume by 22%. Therefore, site-specific Cys insertion on the **Hb** surface results in uniform size **polymers** that do not produce the large

pressor response seen with **tetrameric Hb.** **Polymerization** maintains physiologically relevant oxygen and heme affinity, **stability** toward denaturation and oxidation, and effective oxygen delivery as indicated by reduced cerebral ischemic damage.

L122 ANSWER 73 OF 77 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1990:20098068 BIOTECHNO
TITLE: Enhanced polymerization of recombinant human deoxyhemoglobin β6 Glu→Ile
AUTHOR: Baudin-Chich V.; Pagnier J.; Marden M.; Bohn B.; Lacaze N.; Kister J.; Schaad O.; Edelstein S.J.; Poyart C.
CORPORATE SOURCE: Unite 299 Institut National de la Sante et de la Recherche Medicale, Hopital de Bicetre, F94275 Le Kremlin-Bicetre, France.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, **(1990)**, 87/5 (1845-1849)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ED 20000202
AB **Polymerization** of the deoxy form of sickle cell **hemoglobin** (**Hb** S; β6 Glu→Val) involves both hydrophobic and electrostatic intermolecular contacts. These interactions drive the mutated molecules into long fibrous rods composed of seven pairs of strands. X-ray crystallography of Hb S and electron microscopy image reconstruction of the fibers have revealed the remarkable complementarity between one of the β6 valines of each molecule (the donor site) and an acceptor site at the EF corner of a neighboring tetramer. This interaction constitutes the major lateral contact between the two strands in a pair. To estimate the relative importance of this key hydrophobic contact in **polymer** formation we have generated a **polymerizing Hb** with isoleucine at the β6 position (βE6I) by site-directed mutagenesis. The mutated β chains were produced in Escherichia coli and reassembled into functional **tetramers** with native α chains. Compared to native **Hb** S, the βE6I mutant **polymerizes** faster and with a shortened delay **time** in 1.8 M phosphate buffer, indicating an increased **stability** of the nuclei preceding fiber growth. The solubility of the βE6I mutant **Hb** is half that of native Hb S. Computer modeling of the donor-acceptor interaction shows that the presence of an isoleucine side chain at the donor site induces increased contacts with the receptor site and an increased buried surface area, in agreement with the higher hydrophobicity of the isoleucine residue. The agreement between the predicted and experimental differences in solubility suggests that the transfer of the β6 valine or isoleucine side chain from water to a hydrophobic environment is sufficient to explain the observations.

L122 ANSWER 74 OF 77 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-33217 DRUGU T S
TITLE: RBC substitutes: perfluorocarbon emulsions and hemoglobin solutions.
AUTHOR: Remy B; Deby Dupont G; D'Ans V; Ernest P; Lamy M
CORPORATE SOURCE: Univ.Liege
LOCATION: Liege, Belg.

SOURCE: Ann.Fr.Anesth.Reanim. (18, No. 2, 211-24, 1999) 7 Fig. 3 Tab. 76 Ref.
CODEN: AFAREO ISSN: 0750-7658
AVAIL. OF DOC.: Departement d'anesthesie-reanimation, centre hospitalier universitaire du Sart Tilman, domaine du Sart Tilman, 4000 Liege, Belgium.
LANGUAGE: French
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Use of perfluorocarbon emulsions and hemoglobin solutions as RBC substitutes is reviewed. General characteristics, potential clinical applications, efficacy and possible adverse effects of perfluorocarbon emulsions and **Hb** solutions (human, bovine, recombinant, modified, **stabilized**, and liposome encapsulated **tetrameric Hb**) are discussed.

L122 ANSWER 75 OF 77 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-27225 DRUGU P T S
TITLE: Red blood cell substitutes: current status.
AUTHOR: Jones J A
LOCATION: London, U.K.
SOURCE: Br.J.Anaesth. (74, No. 6, 697-703, 1995) 3 Fig. 3 Tab. 53 Ref.
CODEN: BJANAD ISSN: 0007-0912
AVAIL. OF DOC.: Department of Anaesthetics, St Mary's Hospital, London W2, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The current status of RBC substitutes including Hb solutions and perfluoro compounds (e.g. Fluosol-DA and Perflubron) is reviewed. Methods for prolonging the half-life of Hb, side-effects of Hb solutions and efficacy are detailed. Possible applications of RBC substitutes are discussed.

L122 ANSWER 76 OF 77 DISSABS COPYRIGHT (C) 2006 ProQuest Information and Learning Company; All Rights Reserved on STN
ACCESSION NUMBER: 2000:4257 DISSABS Order Number: AAI9936183
TITLE: HETEROGENEOUS NUCLEATION OF SICKLE HEMOGLOBIN: STRUCTURAL MODELING AND EXPERIMENTAL EVIDENCE (GELATION)
AUTHOR: MIRCHEV, ROSSEN STOYKOV [PH.D.]; FERRONE, FRANK [adviser]
CORPORATE SOURCE: DREXEL UNIVERSITY (0065)
SOURCE: Dissertation Abstracts International, (**1999**) Vol. 60, No. 6B, p. 2565. Order No.: AAI9936183. 93 pages.
DOCUMENT TYPE: Dissertation
FILE SEGMENT: DAI
LANGUAGE: English
AB Sickle **Hemoglobin** molecules assemble into **polymers** composed of seven helically twisted double strands. Intermolecular contacts within the double strands are well established. We show that the same contact sites are present at the polymer surface on four molecules in each layer, and demonstrate that the identical contact geometry can be achieved between fibers. This provides a structural rationale for the exponential polymer growth that characterizes the kinetics of gelation. This also gives a structural basis for the cross-linking which solidifies the gel. The **thermodynamical** characteristics of polymerization are elucidated by the double nucleation model, which assumes two ways of polymerization--homogeneous and heterogeneous. Introducing the predictions

from our structural model into the theoretical description of the double nucleation model, we develop a new way of data analysis for calculation of the heterogeneous nucleation rate, the size of the nucleus, and the heterogeneous nucleation sites availability. This is verified against results from Sickle Hemoglobin experiments. Having the theoretical tools, we test the viability of our model experimentally. Since the mutation is on both b -chains of the Sickle **Hemoglobin tetramer**, replacement of one of them with normal b -chain will reduce the number of polymerization sites but not inhibit gelation. We measure the nucleation rates of **Hemoglobin** with one normal and one mutant b -chain, cross-linked for **stability.** The results show twofold increase of the nucleus size, 103-104 **times** smaller homogeneous nucleation rate, 102-103 **times** smaller heterogeneous nucleation rate, and significant decrease with strong **temperature** dependence of the heterogeneous nucleation site availability which varies 14 orders of magnitude over a 10°C **temperature** range.

L122 ANSWER 77 OF 77 DISSABS COPYRIGHT (C) 2006 ProQuest Information and Learning Company; All Rights Reserved on STN

ACCESSION NUMBER: 1999:25570 DISSABS Order Number: AAI9912367
TITLE: RECOMBINANT HEMOGLOBIN VARIANTS: STRUCTURE-FUNCTION ANALYSIS AND OXYGEN THERAPEUTIC DESIGN (BLOOD SUBSTITUTES)
AUTHOR: SANDERS, KEVIN EUGENE [PH.D.]; SLIGAR, STEPHEN G. [adviser]
CORPORATE SOURCE: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN (0090)
SOURCE: Dissertation Abstracts International, (**1998**) Vol. 59, No. 11B, p. 5840. Order No.: AAI9912367. 129 pages.
DOCUMENT TYPE: Dissertation
FILE SEGMENT: DAI
LANGUAGE: English

AB Recombinant hemoglobin expression provides an invaluable tool to address fundamental scientific issues about hemoglobin and the ability to design improved oxygen carrying therapeutics. By monitoring nanosecond geminate recombination, I have identified a kinetic equivalent to the quaternary enhancement effect, described previously by Ackers and coworkers. The calculated ΔΔG of -450 ± 100 cal/mol, compares favorably with that reported by Ackers of -250 ± 200 cal/mol. Furthermore, mutation of β37trp, a residue positioned in the α1β2 interface, eliminates or reduces the magnitude of the quaternary enhancement effect through destabilization of the **hemoglobin tetramer** and disruption of intersubunit communication.

In addition to structure/function studies within the **hemoglobin tetramer**, I have exploited the **hemoglobin** expression system in the development of **polymeric hemoglobin** like proteins. High molecular weight **polymerized hemoglobins**, designed as oxygen carrying therapeutics, exhibit longer vascular retention and reduced side effects when compared to stabilized tetramers. I have built a circularly permuted α globin sequence via linkage of the original termini with another α globin sequence. The in vivo assembly of this Diα globin with β globins results in a circularly permuted hemoglobin which is crosslinked twice across the dimeric interface and has surface exposed termini amenable to protein fusions. Tandem fusions of the Diα sequence were then created to generate octomeric and dodecameric **hemoglobins.** Each protein assembles into the expected **oligomeric** structures and quantitatively binds heme. Circular dichroism measurements demonstrate the similarity in secondary structure and UV-Vis spectroscopy suggests the heme environments are nearly identical. The variants maintain cooperative oxygen binding, with a Hill coefficients of two and respond to allosteric effectors. The only

significant difference is a five fold increase in the oxygen affinity.

In a rat model each protein exhibited an increased vascular lifetime and no renal excretion. Furthermore, a dose dependent increase in vascular lifetime was observed suggesting that the protein clearance mechanism is saturatable. These circularly permuted variants represent the first recombinantly designed **polymerized hemoglobin.** The clear structural and functional similarity of these variants to native **hemoglobin** and improved vascular **stability** suggests that they have potential for use as an oxygen carrying therapeutic.

```
=> d que stat l18
L3              QUE  ABB=ON  PLU=ON  AVELLA, A?/AU
L4              QUE  ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5              QUE  ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L8              QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9              QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10             QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                 OR (4(W)MER)
L16          89 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L17          18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND L8
L18           9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND (L9 OR L10)


=> d que stat l47
L3              QUE  ABB=ON  PLU=ON  AVELLA, A?/AU
L4              QUE  ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5              QUE  ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L46          10 SEA FILE=WPIX ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L47           5 SEA FILE=WPIX ABB=ON  PLU=ON  L46 AND (HEMOGLOB?/BIX OR
                 HAEMOGLOB?/BIX OR HB/BIX)


=> d que stat l67
L3              QUE  ABB=ON  PLU=ON  AVELLA, A?/AU
L4              QUE  ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5              QUE  ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L8              QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9              QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10             QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                 OR (4(W)MER)
L15             QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L62          65 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L63          17 SEA FILE=MEDLINE ABB=ON  PLU=ON  L62 AND L8
L64           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L63 AND L10
L65           2 SEA FILE=MEDLINE ABB=ON  PLU=ON  L63 AND (L15 OR PRESERV?)
L66           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  L63 AND L9
L67           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L64 OR L65 OR L66)


=> d que stat l89
L3              QUE  ABB=ON  PLU=ON  AVELLA, A?/AU
L4              QUE  ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5              QUE  ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L8              QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9              QUE  ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10             QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                 OR (4(W)MER)
L15             QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L87          47 SEA FILE=EMBASE ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L88          12 SEA FILE=EMBASE ABB=ON  PLU=ON  L87 AND L8
L89           5 SEA FILE=EMBASE ABB=ON  PLU=ON  L88 AND (L9 OR L10 OR L15)


=> d his l113

     (FILE 'BIOSIS, PASCAL, JICST-EPLUS, BIOENG, LIFESCI, CABA, BIOTECHNO,
     BIOTECHDS, VETU, VETB, DRUGU, DRUGB, SCISEARCH, CONF, CONFSCI, DISSABS'
     ENTERED AT 10:12:38 ON 12 MAY 2006)
L113            3 S L111 OR L112
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=> d que stat l113
L3               QUE  ABB=ON  PLU=ON  AVELLA, A?/AU
L4               QUE  ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5               QUE  ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L8               QUE  ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L10              QUE  ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER
                  OR (4(W)MER)
L15              QUE  ABB=ON  PLU=ON  STABILI? OR STABL?
L109         259 SEA (L3 OR L4 OR L5)
L110          35 SEA L109 AND L8
L111           1 SEA L110 AND L15
L112           2 SEA L110 AND L10
L113           3 SEA L111 OR L112


=> dup rem l18 l47 l67 l89 l113
DUPLICATE IS NOT AVAILABLE IN 'CONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 10:36:05 ON 12 MAY 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'MEDLINE' ENTERED AT 10:36:05 ON 12 MAY 2006

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FILE 'BIOSIS' ENTERED AT 10:36:05 ON 12 MAY 2006
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PROCESSING COMPLETED FOR L18
PROCESSING COMPLETED FOR L47
PROCESSING COMPLETED FOR L67
PROCESSING COMPLETED FOR L89
PROCESSING COMPLETED FOR L113
L123          15 DUP REM L18 L47 L67 L89 L113 (12 DUPLICATES REMOVED)
                 ANSWERS '1-9' FROM FILE HCAPLUS
                 ANSWER '10' FROM FILE WPIX
                 ANSWERS '11-12' FROM FILE MEDLINE
                 ANSWER '13' FROM FILE EMBASE
                 ANSWERS '14-15' FROM FILE BIOSIS

=> file stnguide
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May  5, 2006 (20060505/UP).

=> d ibib ed ab 1-15
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS' -
CONTINUE? (Y)/N:y
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L123 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:648348 HCAPLUS
DOCUMENT NUMBER: 141:179552
TITLE: Preparation of **polymerized hemoglobin** solutions having reduced amount of **tetramer**
INVENTOR(S): **Avella, Anthony; Dewoskin, Richard E.; Doubleday, Marc D.**
PATENT ASSIGNEE(S): Northfield Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004066953	A2	20040812	WO 2004-US2512	20040129
WO 2004066953	A3	20050407		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
AU 2004207595	A1	20040812	AU 2004-207595	20040129
CA 2512169	AA	20040812	CA 2004-2512169	20040129
US 2004186047	A1	20040923	US 2004-767516	20040129
EP 1592437	A2	20051109	EP 2004-706483	20040129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004007106	A	20060124	BR 2004-7106	20040129
CN 1741813	A	20060301	CN 2004-80002922	20040129
NO 2005003745	A	20051003	NO 2005-3745	20050804
PRIORITY APPLN. INFO.:			US 2003-443436P P	20030129
			WO 2004-US2512 W	20040129

ED Entered STN: 12 Aug 2004
AB A method for producing a substantially **tetramer**-free **Hb** solution is described. The method includes (i) **polymerizing** a solution of **Hb**, (ii) treating the **polymerized Hb** solution to partially degrade the **polymer** to **tetramer**, e.g., by heating the **Hb** solution above about 45° for at least 24 h, and (iii) removing **tetramer** from the **Hb** solution by filtration. The **Hb** may be derived from mammalian blood, such as human or bovine blood.

L123 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:293378 HCAPLUS
DOCUMENT NUMBER: 140:264506
TITLE: Method for treating patients with massive blood loss
INVENTOR(S): Gould, Steven A.; **Dewoskin, Richard E.; Doubleday, Marc D.**; Hides, George A.
PATENT ASSIGNEE(S): Northfield Laboratories, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2004067876	A1	20040408	US 2003-678927	20031003
CA 2499459	AA	20040506	CA 2003-2499459	20031003
WO 2004037279	A1	20040506	WO 2003-US31377	20031003
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003272827	A1	20040513	AU 2003-272827	20031003
EP 1553968	A1	20050720	EP 2003-755029	20031003
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006502231	T2	20060119	JP 2004-546786	20031003
NO 2005001390	A	20050530	NO 2005-1390	20050316
ZA 2005002307	A	20051004	ZA 2005-2307	20050318
PRIORITY APPLN. INFO.:			US 2002-415935P	P 20021003
			WO 2003-US31377	W 20031003

ED Entered STN: 09 Apr 2004
AB Methods for treating a mammal suffering from massive blood loss comprising administering to the mammal a **polymerized Hb** solution

L123 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2002:832532 HCAPLUS
DOCUMENT NUMBER: 137:329404
TITLE: Flexible container system for storage of stabilized **hemoglobin** solutions
INVENTOR(S): McGinnis, Robert L.; Chavez, Gabriel; **Doubleday, Marc; Dewoskin, Richard; Avella, Anthony**
PATENT ASSIGNEE(S): Northfield Laboratories, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085111	A1	20021031	WO 2002-US12118	20020418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2444590	AA	20021031	CA 2002-2444590	20020418
US 2003065149	A1	20030403	US 2002-124941	20020418
EP 1381274	A1	20040121	EP 2002-723885	20020418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

CN 1516550	A	20040728	CN 2002-812135	20020418
JP 2004538264	T2	20041224	JP 2002-582703	20020418
US 2006014671	A1	20060119	US 2005-231921	20050921
PRIORITY APPLN. INFO.:			US 2001-284651P	P 20010418
			US 2002-124941	B1 20020418
			WO 2002-US12118	W 20020418

ED Entered STN: 01 Nov 2002

AB A **Hb** solution packaged in a flexible oxygen-impermeable container system. The container system includes a multi-layer film having at least a product contact layer, an oxygen and moisture barrier layer and an exterior layer. The flexible container system further includes an interface port for filling the flexible container with the **Hb** solution and delivering the **Hb** solution The **Hb** solution comprises a substantially stroma and **tetramer** free, cross linked, pyridoxylated **Hb** solution including preservatives such as ascorbic acid, glycine and dextrose.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L123 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 1997:650369 HCAPLUS

DOCUMENT NUMBER: 127:311442

TITLE: Method and apparatus for preparing an acellular red blood cell substitute

INVENTOR(S): **DeWoskin, Richard E.; Doubleday, Marc D.**

PATENT ASSIGNEE(S): Northfield Laboratories, Inc., USA; DeWoskin, Richard E.; Doubleday, Marc D.

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9735883	A1	19971002	WO 1997-US5088	19970327
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2250274	AA	19971002	CA 1997-2250274	19970327
CA 2250274	C	20030916		
AU 9724253	A1	19971017	AU 1997-24253	19970327
AU 740210	B2	20011101		
CN 1219939	A	19990616	CN 1997-194998	19970327
CN 1129608	B	20031203		
EP 928294	A1	19990714	EP 1997-919943	19970327
EP 928294	B1	20030528		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9708388	A	20000104	BR 1997-8388	19970327
JP 2000507947	T2	20000627	JP 1997-534650	19970327
NZ 332067	A	20010330	NZ 1997-332067	19970327
AP 1028	A	20011130	AP 1998-1353	19970327

W: GM, GH, KE, LS, MW, SD, SZ, UG, ZW

RU 2203087	C2	20030427	RU 1998-119535		19970327
EP 1308460	A2	20030507	EP 2003-277		19970327
EP 1308460	A3	20030813			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, AL					
AT 241646	E	20030615	AT 1997-919943		19970327
PT 928294	T	20031031	PT 1997-919943		19970327
ES 2200177	T3	20040301	ES 1997-919943		19970327
PL 187923	B1	20041130	PL 1997-329108		19970327
NO 9804473	A	19981125	NO 1998-4473		19980925
KR 2000005058	A	20000125	KR 1998-707685		19980928
BG 63919	B1	20030630	BG 1998-102810		19981001
US 2002025343	A1	20020228	US 1999-155419		19990510
US 6498141	B2	20021224			
US 2003191050	A1	20031009	US 2002-274099		20021017
US 2005065067	A1	20050324	US 2004-993228		20041119
PRIORITY APPLN. INFO.:			US 1996-14389P	P	19960328
			EP 1997-919943	A3	19970327
			WO 1997-US5088	W	19970327
			US 1999-155419	A1	19990510
			US 2002-274099	B1	20021017

ED Entered STN: 13 Oct 1997

AB A process is disclosed for preparation of an essentially **tetramer**-free, substantially stroma-free, **polymerized**, pyridoxylated **Hb** product capable of being infused into human patients in an amount of ≤5 L. This product does not show the toxicity associated with the presence of **Hb tetramers** and stroma, has a substantial half-life of ≥15 h in the blood, and is capable of reversibly transporting O to the tissues. Thus, erythrocytes from outdated blood were filtered to remove leukocytes and platelets, washed under a CO atmospheric, and hemolyzed by addition of water. The solution was diafiltered, heat treated at 60-62° for .apprx.10 h, degassed, and the protein was pyridoxylated with pyridoxal 5'-phosphate in the presence of NaBH4 and crosslinked with glutaraldehyde. The crosslinking reaction was terminated by addition of aqueous glycine buffer, and the crosslinks were stabilized with aqueous NaBH4. The product had a mol. weight predominantly in the 100,000-350,000 range and contained 4.6% metHb, 0.2% carboxyHb, and 0.4% **tetramer.** Apparatus for carrying out the process is described.

L123 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER:	1997:624794 HCAPLUS
DOCUMENT NUMBER:	127:272546
TITLE:	Clinical utility of human **polymerized hemoglobin** as a blood substitute after acute trauma and urgent surgery
AUTHOR(S):	Gould, Steven A.; Moore, Ernest E.; Moore, Frederick A.; Haenel, James B.; Burch, Jon M.; Sehgal, Hansa; Sehgal, Lakshman; **Dewoskin, Richard**; Moss, Gerald S.
CORPORATE SOURCE:	Department of Surgery, Michael Reese Hospital and University of Illinois, Chicago, IL, USA
SOURCE:	Journal of Trauma: Injury, Infection, and Critical Care (1997), 43(2), 325-332 CODEN: JOTRFA; ISSN: 1079-6061
PUBLISHER:	Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

ED Entered STN: 01 Oct 1997

AB We have previously documented the safety of 1 unit (50 g) of human **polymerized Hb** (Poly SFH-P) in healthy volunteers. This report describes the first patient trial to assess the therapeutic benefit of Poly SFH-P in acute blood loss. Thirty-nine patients received 1 (n = 14), 2 (n = 2), 3 (n = 15), or 6 (n = 8) units of Poly SFH-P instead of red cells as part of their blood replacement after trauma and urgent surgery. There were no safety issues related to the infusion of Poly SFH-P. The plasma **Hb** concentration ([**Hb**]) after the infusion of 6 units (300 g) of Poly SFH-P was 4.8 ± 0.8 g/dL (mean ± SD). Although the red cell [**Hb**] fell to 2.9 ± 1.2 g/dL, the total [**Hb**] was maintained at 7.5 ± 1.2 g/dL. Poly SFH-P maintained total [**Hb**], despite the marked fall in red cell [**Hb**] due to blood loss. The utilization of O2 (extraction ratio) was 27 ± 16% from the red cells and 37 ± 13% from the Poly SFH-P. Twenty-three patients (59%) avoided allogeneic transfusions during the first 24 h after blood loss. Poly SFH-P effectively loads and unloads O2 and maintains total **Hb** in lieu of red cells after acute blood loss, thereby reducing allogeneic transfusions. Poly SFH-P seems to be a clin. useful blood substitute.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L123 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1990:232936 HCAPLUS
DOCUMENT NUMBER: 112:232936
TITLE: Effect of **hemoglobin** solution on compensation to anemia in the erythrocyte-free primate
AUTHOR(S): Rosen, Arthur L.; Gould, Steven A.; Sehgal, Lakshman R.; Sehgal, Hansa L.; Levine, Harry D.; **DeWoskin, Richard D.**; Moss, Gerald S.
CORPORATE SOURCE: Dep. Surg., Michael Reese Hosp. Med. Cent., Chicago, IL, 60616, USA
SOURCE: Journal of Applied Physiology (1990), 68(3), 938-43
CODEN: JAPHEV; ISSN: 8750-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Jun 1990
AB **Hb** solns. are undergoing clin. trials as erythrocyte substitutes. Some of these solns. have high O2 affinities compared with normal erythrocyte **Hb.** Also, they appear to interact with endothelial-derived smooth muscle relaxation. The purpose of this study was to evaluate the nature and limits of compensation to acute normovolemic anemia in the erythrocyte-free primate maintained with **Hb** solution The exptl. group consisted of six anesthetized paralyzed adult baboons (Papio anubis) that were exchange transfused (ET) with a pyridoxylated **polymerized Hb** solution {**Hb** concentration ([**Hb**]) = 14 g/dL, O2 half-saturation pressure of **Hb** (P50) = 19.6 Torr} until a hematocrit <1% was achieved. They underwent a second ET with Dextran-70 until [**Hb**] = 1 g/dL. A control group underwent an ET with Dextran-70 until [**Hb**] = 1 g/dL. Both groups maintained O2 consumption (VO2) until [**Hb**] = 3 g/dL. Both groups were stable until [**Hb**] <1 g/dL, and both groups increased their cardiac output. The relation between VO2 and O2 delivery was similar for both groups. In vivo P50 and mixed venous O2 tension were lower in the exptl. group. The nature and limits of compensation to diminished O2 delivery due to anemia were similar in the two groups.

L123 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1988:597119 HCAPLUS
DOCUMENT NUMBER: 109:197119

TITLE: Characteristics of **polymerized** pyridoxylated **hemoglobin**
AUTHOR(S): Sehgal, L. R.; Sehgal, H. L.; Rosen, A. L.; Gould, S. A.; **DeWoskin, R.**; Moss, G. S.
CORPORATE SOURCE: Med. Cent., Michael Reese Hosp., Chicago, IL, 60616, USA
SOURCE: Biomaterials, Artificial Cells, and Artificial Organs (1988), 16(1-3), 173-83
CODEN: BACOEZ; ISSN: 0890-5533
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 25 Nov 1988
AB **Polymerization** of pyridoxylated stroma-free **Hb** currently provides the only approach that leads to a **Hb** solution that approximates the O carrying capacity of whole blood and can be infused without altering the colloid osmotic pressure of plasma. It appears to have an adequate O loading and unloading characteristic and a greatly improved intravascular half-life. In addition stable shelf-life at 4° of >5 mo, makes it a prime candidate for future preclin. and clin. investigations.

L123 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:305698 HCAPLUS
DOCUMENT NUMBER: 129:144499
TITLE: The clinical development of human **polymerized hemoglobin**
AUTHOR(S): Gould, Steven A.; Sehgal, Lakshman R.; Sehgal, Hansa L.; **Dewoskin, Richard**; Moss, Gerald S.
CORPORATE SOURCE: Northfield Laboratories, Inc., Evanston, IL, USA
SOURCE: Blood Substitutes (1998), Volume 2, 12-38. Editor(s): Chang, Thomas Ming Swi. Karger Landes Systems: Basel, Switz.
CODEN: 66ALAF
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
ED Entered STN: 25 May 1998
AB A review with 37 refs. Development of **polymerized** form of **Hb** that is virtually free of unreacted **tetramer** is described. Phase I and II clin. trials demonstrated preliminary evidence of the safety and efficacy of **polymerized Hb** as a clin. useful red cell substitute in the acute blood loss in the setting of trauma and surgery.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L123 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:121365 HCAPLUS
DOCUMENT NUMBER: 110:121365
TITLE: Acellular erythrocyte substituent comprising pyridoxylated **polymerized hemoglobin** free of stroma
INVENTOR(S): Sehgal, Lakshman R.; **DeWoskin, Richard E.**; Moss, Gerald S.; Gould, Steven A.; Rosen, Arthur L.; Sehgal, Hansa
PATENT ASSIGNEE(S): Northfield Laboratories, Inc., USA
SOURCE: Fr. Demande, 50 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2600255	A1	19871224	FR 1987-8639	19870619
FR 2600255	B1	19900727		
US 4826811	A	19890502	US 1986-876689	19860620
WO 8707832	A1	19871230	WO 1987-US1372	19870612
W: DE, GB, JP, NL				
RW: IT				
NL 8720283	A	19880502	NL 1987-20283	19870612
NL 194909	B	20030303		
NL 194909	C	20030704		
EP 271542	A1	19880622	EP 1987-903990	19870612
EP 271542	B1	19910904		
R: IT				
DE 3790322	T	19880915	DE 1987-3790322	19870612
DE 3790322	C2	19990902		
JP 01501471	T2	19890525	JP 1987-503558	19870612
JP 2983544	B2	19991129		
IL 82890	A1	19920216	IL 1987-82890	19870616
CA 1298783	A1	19920414	CA 1987-540186	19870619
GB 2200639	A1	19880810	GB 1988-1735	19880127
GB 2200639	B2	19901212		
US 5194590	A	19930316	US 1990-616727	19901121
US 6133425	A	20001017	US 1993-31563	19930315
US 5464814	A	19951107	US 1994-203505	19940228
US 5747649	A	19980505	US 1995-484942	19950607
US 6323320	B1	20011127	US 2000-638471	20000814
US 2002062007	A1	20020523	US 2001-995203	20011127
US 6552173	B2	20030422		
US 2003130487	A1	20030710	US 2003-348579	20030121
US 6914127	B2	20050705		

PRIORITY APPLN. INFO.:		
US 1986-876689	A	19860620
WO 1987-US1372	A	19870612
US 1989-315130	B1	19890223
US 1989-345416	B1	19890428
US 1990-616727	A1	19901121
US 1992-896734	B1	19920609
US 1993-31563	A1	19930315
US 1995-484942	A1	19950607
US 2000-638471	A1	20000814
US 2001-995203	A1	20011127

ED Entered STN: 03 Apr 1989

AB An acellular erythrocyte substituent comprises pyridoxylated cross-linked **polymerized Hb**, free of **tetramer** and of stroma, as well a pharmaceutically acceptable nontoxic support. Human erythrocytes, washed with antibiotics-containing physiol. saline, were hemolyzed in water, followed by ultrafiltration on hollow fibers, and concentration of the ultrafiltrate to 20-22 g **Hb**/dL. This was treated with a solution (pH 7.25-7.45) containing pyridoxal-5'-phosphate, glutathion, ascorbic acid, glucose, tris-HCl buffer and antibiotics, followed by deoxygenation, treatment with NaBH4, and by removal of the excess reagents using a renal dialysis filter. The stroma-free pyridoxylated **Hb** obtained was **polymerized** by contact, through a dialysis filter, with a circulating glutaraldehyde solution, added to system, over 7 h, in a programmed manner. The **polymerized** pyridoxylated **Hb** was purified by ultrafiltration, gel filtration, and affinity chromatog. on agarose gel-bound haptoglobin.

L123 ANSWER 10 OF 15 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1988-014337 [02] WPIX
CROSS REFERENCE: 1993-109383 [13]; 1995-402845 [51]
DOC. NO. CPI: C1988-006256
TITLE: New tetramer-free acellular red blood cell substitute - showing no decrease in urine production and glomerular filtration rate.
DERWENT CLASS: A96 B04
INVENTOR(S): **DEWOSKIN, R E**; GOULD, S A; MOSS, G S; ROSEN, A L; SEHGAL, H L; SEHGAL, L R; DE WOSKIN, R E; SEHGAL, H; WOSKIN, R E
PATENT ASSIGNEE(S): (NORT-N) NORTHFIELD LAB; (NORH-N) NORTHFIELD LAB INC
COUNTRY COUNT: 11
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 8707832	A	19871230	(198802)*	EN	48
RW: IT					
W: DE GB JP NL					
FR 2600255	A	19871224	(198807)		
NL 8720283	A	19880502	(198821)		
EP 271542	A	19880622	(198825)	EN	
R: IT					
PT 85133	A	19880701	(198831)		
GB 2200639	A	19880810	(198832)		
DE 3790322	T	19880915	(198838)		
US 4826811	A	19890502	(198920)		21
JP 01501471	W	19890525	(198927)		
ES 2007640	A	19890701	(198947)		
GB 2200639	B	19901212	(199050)		
EP 271542	B	19910904	(199136)		
R: IT					
IL 82890	A	19920216	(199220)		
CA 1298783	C	19920414	(199224)		
US 5747649	A	19980505	(199825)		
DE 3790322	C2	19990902	(199939)		
JP 2983544	B2	19991129	(200002)		18
US 6133425	A	20001017	(200054)		
US 6323320	B1	20011127	(200175)		
US 2002062007	A1	20020523	(200239)		
NL 194909	B	20030303	(200319)		
US 6552173	B2	20030422	(200330)		
US 2003130487	A1	20030710	(200347)		
NL 194909	C	20030704	(200366)		
US 6914127	B2	20050705	(200544)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 8707832	A	WO 1987-US1372	19870612
FR 2600255	A	FR 1987-8639	19870619
NL 8720283	A	NL 1987-20283	19870612
EP 271542	A	EP 1987-903990	19870612
GB 2200639	A	GB 1987-1735	19870612
DE 3790322	T	DE 1987-3790322	19871230
US 4826811	A	US 1986-876689	19860620
JP 01501471	W	JP 1987-503558	19870612
ES 2007640	A	ES 1987-2036	19870710

IL 82890	A	IL 1987-82890	19870616
CA 1298783	C	CA 1987-540186	19870619
US 5747649	A Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
		US 1995-484942	19950607
DE 3790322	C2	DE 1987-3790322	19870612
		WO 1987-US1372	19870612
JP 2983544	B2	JP 1987-503558	19870612
		WO 1987-US1372	19870612
US 6133425	A Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
		US 1993-31563	19930315
US 6323320	B1 Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
		US 2000-638471	20000814
US 2002062007	A1 Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
	Cont of	US 2000-638471	20000814
		US 2001-995203	20011127
NL 194909	B	NL 1987-20283	19870612
		WO 1987-US1372	19870612
US 6552173	B2 Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
	Cont of	US 2000-638471	20000814
		US 2001-995203	20011127
US 2003130487	A1 Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
	Cont of	US 2000-638471	20000814
	Cont of	US 2001-995203	20011127
		US 2003-348579	20030121
NL 194909	C	NL 1987-20283	19870612
US 6914127	B2 Cont of	US 1986-876689	19860620
	Cont of	US 1989-315130	19890223
	Cont of	US 1990-616727	19901121
	Cont of	US 1993-31563	19930315
	Cont of	US 1995-484942	19950607
	Cont of	US 2000-638471	20000814
	Cont of	US 2001-995203	20011127
		US 2003-348579	20030121

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 5747649	A Cont of	US 4826811
	Cont of	US 5194590
DE 3790322	C2 Based on	WO 8707832
JP 2983544	B2 Previous Publ.	JP 01501471
	Based on	WO 8707832

US 6133425	A	Cont of	US 4826811
		Cont of	US 5194590
US 6323320	B1	Cont of	US 4826811
		Cont of	US 5194590
		Cont of	US 6133425
NL 194909	B	Based on	WO 8707832
US 6552173	B2	Cont of	US 4826811
		Cont of	US 5194590
		Cont of	US 6133425
		Cont of	US 6323320
US 2003130487	A1	Cont of	US 4826811
		Cont of	US 5194590
		Cont of	US 6133425
		Cont of	US 6323320
		Cont of	US 6552173
US 6914127	B2	Cont of	US 4826811
		Cont of	US 5194590
		Cont of	US 5747649
		Cont of	US 6133425
		Cont of	US 6323320
		Cont of	US 6552173

PRIORITY APPLN. INFO: US 1986-876689 19860620; ES
1987-2036 19870710; US
1989-315130 19890223; US
1990-616727 19901121; US
1993-31563 19930315; US
1995-484942 19950607; US
2000-638471 20000814; US
2001-995203 20011127; US
2003-348579 20030121

ED 19930803

AB WO 8707832 A UPAB: 20050712
An acellular red blood cell (RBC) substitute (I) comprises a tetramer-free, stroma-free, cross-linked, polymerised, pyridoxylated **haemoglobin** and a carrier. Preparation of (I) is also claimed.
USE/ADVANTAGE - The following iv. uses of (I)are all listed in the claims: (1) treatment of trauma; (2) treatment of acute anaemia; (3) any disease or medical condition requiring a resuscitative fluid or iv vol expander; (4) exchange transfusion of an acellular RBC substitute; and (5) treatment of an oxygen deficiency disorder, e.g. hypoxia or hypoxemia. This temporary oxygen carrier is rendered free of microbial and viral antigens and pathogens. (I) shows reversible oxygen binding capacities which will not require compatibility studies with a recipient. The **haemoglobin** in (I) is free of vasoconstrictive activity and produces no appreaciable decrease in urine production nor glomerular filtration rate. There is no appreciable extra-vasation into the peritoneal cavity nor change in the colour of urine produced.
0/11
Dwg.0/11

L123 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002618512 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12375748
TITLE: The life-sustaining capacity of human **polymerized hemoglobin** when red cells might be unavailable.
AUTHOR: Gould Steven A; Moore Ernest E; Hoyt David B; Ness Paul M; Norris Edward J; Carson Jeffrey L; Hides George A; Freeman Ian H G; **DeWoskin Richard**; Moss Gerald S
CORPORATE SOURCE: Northfield Laboratories Inc., Evanston, IL, USA.

SOURCE: Journal of the American College of Surgeons, (2002 Oct) Vol. 195, No. 4, pp. 445-52; discussion 452-5. Journal code: 9431305. ISSN: 1072-7515.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 12 Oct 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 3 Dec 2002

ED Entered STN: 12 Oct 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 3 Dec 2002

AB BACKGROUND: Human **polymerized hemoglobin** (PolyHeme, Northfield Laboratories, Evanston, IL) is a universally compatible, immediately available, disease-free, oxygen-carrying resuscitative fluid being developed as a red cell substitute for use in urgent blood loss. PolyHeme should be particularly useful when red cells may be temporarily unavailable. This article assesses survival at life-threatening RBC **hemoglobin** concentration ([**Hb**]) in massively bleeding patients who do not receive red cells. STUDY DESIGN: There were 171 patients who received rapid infusion of 1 to 20 units (1,000 g, 10 L) of PolyHeme in lieu of red cells as initial oxygen-carrying replacement in trauma and urgent surgery. The protocol simulated the unavailability of red cells, and the progressive fall in RBC [**Hb**] in bleeding patients was quantified. Thirty-day mortality was compared with a historical control group of 300 surgical patients who refused red cells on religious grounds. RESULTS: A total of 171 patients received rapid infusion of 1 to 2 units (n = 45), 3 to 4 units (n = 45), 5 to 9 units (n = 47), or 10 to 20 units (n = 34) of PolyHeme. Forty patients had a nadir RBC [**Hb**] < or = 3 g/dL (mean, 1.5 +/- 0.7 g/dL). But total [**Hb**] was adequately maintained (mean, 6.8 +/- 1.2 g/dL) because of plasma [**Hb**] added by PolyHeme. The 30-day mortality was 25.0% (10/40 patients) compared with 64.5% (20/31 patients) in historical control patients at these RBC [**Hb**] levels. CONCLUSIONS: PolyHeme increases survival at life-threatening RBC [**Hb**] by maintaining total [**Hb**] in the absence of red cell transfusion. PolyHeme should be useful in the early treatment of urgent blood loss and resolve the dilemma of unavailability of red cells.

L123 ANSWER 12 OF 15 MEDLINE on STN
ACCESSION NUMBER: 1998368653 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9704955
TITLE: The first randomized trial of human **polymerized hemoglobin** as a blood substitute in acute trauma and emergent surgery.
AUTHOR: Gould S A; Moore E E; Hoyt D B; Burch J M; Haenel J B; Garcia J; **DeWoskin R**; Moss G S
CORPORATE SOURCE: University of Illinois, Chicago, USA.
SOURCE: Journal of the American College of Surgeons, (1998 Aug) Vol. 187, No. 2, pp. 113-20; discussion 120-2. Journal code: 9431305. ISSN: 1072-7515.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 3 Sep 1998
Last Updated on STN: 3 Sep 1998
Entered Medline: 27 Aug 1998
ED Entered STN: 3 Sep 1998
Last Updated on STN: 3 Sep 1998
Entered Medline: 27 Aug 1998
AB BACKGROUND: Human **polymerized hemoglobin** (PolyHeme) is a universally compatible, disease-free, oxygen-carrying resuscitative fluid. This is the first prospective, randomized trial to compare directly the therapeutic benefit of PolyHeme with that of allogeneic red blood cells (RBCs) in the treatment of acute blood loss. STUDY DESIGN: Forty-four trauma patients (33 male, 11 female) aged 19-75 years with an average Injury Severity Score (ISS) score of 21+/-10 were randomized to receive red cells (n = 23) or up to 6 U (300 g) of PolyHeme (n = 21) as their initial blood replacement after trauma and during emergent operations. RESULTS: There were no serious or unexpected adverse events related to PolyHeme. The PolyHeme infusion of 4.4+/-2.0 units (mean +/- SD) resulted in a plasma [**Hb**] of 3.9+/-1.3 g/dL, which accounted for 40% of the total circulating [**Hb**]. There was no difference in total [**Hb**] between the groups before infusion (10.4+/-2.3 g/dL control vs. 9.4+/-1.9 g/dL experimental). At end-infusion the experimental RBC [**Hb**] fell to 5.8+/-2.8 g/dL vs. 10.6+/-1.8 g/dL ($p < 0.05$) in the control, although the total [**Hb**] was not different between the groups or from pre-infusion. The total number of allogeneic red cell transfusions for the control and experimental groups was 10.4+/-4.2 units vs. 6.8+/-3.9 units ($p < 0.05$) through day 1, and 11.3+/-4.1 units vs. 7.8 +/-4.2 units ($p = 0.06$) through day 3. CONCLUSIONS: PolyHeme is safe in acute blood loss, maintains total [**Hb**] in lieu of red cells despite the marked fall in RBC [**Hb**], and reduces the use of allogeneic blood. PolyHeme appears to be a clinically useful blood substitute.

L123 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 88142200 EMBASE
DOCUMENT NUMBER: 1988142200
TITLE: Preparation and characteristics of **polymerized** pyridoxylated **hemoglobin.**
AUTHOR: Sehgal L.R.; Rosen A.L.; Gould S.A.; Sehgal H.L.; **DeWoskin R.**; Moss G.S.
CORPORATE SOURCE: Department of Surgery, Mechael Rees Hospital, Chicago, IL, United States
SOURCE: Trasfusione del Sangue, (1988) Vol. 33, No. 2, pp. 110-120.
.
ISSN: 0041-1787 CODEN: TRSABD
COUNTRY: Italy
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991
ED Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991

L123 ANSWER 14 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:280010 BIOSIS
DOCUMENT NUMBER: PREV199800280010

TITLE: The clinical development of human polymerized **hemoglobin.**
AUTHOR(S): Gould, Steven A. [Reprint author]; Sehgal, Lakshman R.; Sehgal, Hansa L.; **Dewoskin, Richard**; Moss, Gerald S.
CORPORATE SOURCE: Northfield Lab. Inc., 1560 Sherman Avenue, Suite 1000, Evanston, IL 60201, USA
SOURCE: Chang, T. M. S. [Editor]. (1998) pp. 12-38. Tissue Engineering; Blood substitutes: Principles, methods, products and clinical trials, Vol. 2. print. Publisher: S. Karger AG, P.O. Box, Allschwilerstrasse 10, CH-4009 Basel, Switzerland; S. Karger AG, New York, New York, USA.
ISBN: 3-8055-6633-6.
DOCUMENT TYPE: Book
Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 1998
Last Updated on STN: 8 Jul 1998
ED Entered STN: 8 Jul 1998
Last Updated on STN: 8 Jul 1998

L123 ANSWER 15 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1988:172959 BIOSIS
DOCUMENT NUMBER: PREV198834087571; BR34:87571
TITLE: ANIMAL MODEL FOR NEPHROTOXICITY OF **HEMOGLOBIN** SOLUTIONS.
AUTHOR(S): ROSEN A L [Reprint author]; SEHGAL L R; GOULD S A; SEHGAL H L; **DEWOSKIN R**; MOSS G S
CORPORATE SOURCE: DEP SURG, MICHAEL REESE HOSP, PRITZKER SCH MED, LAKE SHORE DR AT 31ST ST, CHICAGO, ILL 60616, USA
SOURCE: Biomaterials Artificial Cells and Artificial Organs, (1987) Vol. 15, No. 2, pp. 383.
Meeting Info.: 3RD INTERNATIONAL SYMPOSIUM ON BLOOD SUBSTITUTES, MONTREAL, QUEBEC, CANADA, MAY 26-28, 1987.
BIOMATER ARTIF CELLS ARTIF ORGANS.
CODEN: BACOEZ. ISSN: 0890-5533.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 28 Mar 1988
Last Updated on STN: 28 Mar 1988
ED Entered STN: 28 Mar 1988
Last Updated on STN: 28 Mar 1988

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 10:36:51 ON 12 MAY 2006
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 5, 2006 (20060505/UP).

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=> d his ful

     (FILE 'HOME' ENTERED AT 08:25:38 ON 12 MAY 2006)

     FILE 'ZCAPLUS' ENTERED AT 08:25:46 ON 12 MAY 2006
               E US2004-767516/APPS

     FILE 'HCAPLUS' ENTERED AT 08:26:08 ON 12 MAY 2006
L1             1 SEA ABB=ON  PLU=ON  US2004-767516/APPS

     FILE 'STNGUIDE' ENTERED AT 08:26:26 ON 12 MAY 2006

     FILE 'HCAPLUS' ENTERED AT 08:26:33 ON 12 MAY 2006
               D IBIB ED AB IND

     FILE 'STNGUIDE' ENTERED AT 08:26:34 ON 12 MAY 2006

     FILE 'WPIX' ENTERED AT 08:28:07 ON 12 MAY 2006
L2             1 SEA ABB=ON  PLU=ON  US2004-767516/APPS
               SAVE TEMP L2 MOH516WPIAPP/A
               D IALL CODE

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     FILE 'ZCAPLUS' ENTERED AT 08:34:25 ON 12 MAY 2006
               E A61K035-00/IPC
               E E15+ALL
               E A61K038-00/IPC
               E E73+ALL
               E C07K014-805/IPC
               E E149+ALL

     FILE 'LWPI' ENTERED AT 08:37:51 ON 12 MAY 2006
               E B04-B04D2/MC
               E E169+ALL
               E B10-D01/MC
               E E186+ALL
               E B11-B/MC
               E E210+ALL
               E 201+ALL
               E E201+ALL
               E C14-F01B/MC
               E E236+ALL
               E B14/MC
               E E253
               E E266+ALL

     FILE 'ZCAPLUS' ENTERED AT 08:40:44 ON 12 MAY 2006
L3             QUE ABB=ON  PLU=ON  AVELLA, A?/AU
L4             QUE ABB=ON  PLU=ON  DEWOSKIN, R?/AU
L5             QUE ABB=ON  PLU=ON  DOUBLEDAY, M?/AU
L6             QUE ABB=ON  PLU=ON  (NORTHFIELD OR (NORTH(W)FIELD))/PA,CS,SO
L7             QUE ABB=ON  PLU=ON  AY<2004 OR PY<2004 OR PRY<2004 OR MY<2004
               OR REVIEW/DT
L8             QUE ABB=ON  PLU=ON  HEMOGLOB? OR HAEMOGLOB? OR HB
L9             QUE ABB=ON  PLU=ON  ?POLYMER? OR POLYMD OR ?OLIGOMER?
L10            QUE ABB=ON  PLU=ON  ?TETRAMER? OR (TETRA(W)MER?) OR 4MER OR
               (4(W)MER)
L11            QUE ABB=ON  PLU=ON  ?PYRIDOX?
L12            QUE ABB=ON  PLU=ON  HEAT OR HEATING OR HEATED OR HEATS OR
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                PREHEAT? OR (PRE(W)HEAT?) OR TEMP OR TEMPERATURE
L13             QUE ABB=ON  PLU=ON  AGE OR AGING OR AGEING OR AGES OR AGED OR
                TIME

     FILE 'STNGUIDE' ENTERED AT 08:46:02 ON 12 MAY 2006

     FILE 'ZCAPLUS' ENTERED AT 09:00:15 ON 12 MAY 2006
                E HEMOGLOBINS/CT
                E E330+ALL
L14             QUE ABB=ON  PLU=ON  HEMOGLOBINS+PFT,OLD,NT/CT
L15             QUE ABB=ON  PLU=ON  STABILI? OR STABL?

     FILE 'HCAPLUS' ENTERED AT 09:01:34 ON 12 MAY 2006

     FILE 'STNGUIDE' ENTERED AT 09:01:40 ON 12 MAY 2006

     FILE 'HCAPLUS' ENTERED AT 09:01:59 ON 12 MAY 2006
L16           89 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L17           18 SEA ABB=ON  PLU=ON  L16 AND L8
L18            9 SEA ABB=ON  PLU=ON  L17 AND (L9 OR L10)
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 09:02:52 ON 12 MAY 2006

     FILE 'HCAPLUS' ENTERED AT 09:03:43 ON 12 MAY 2006
                SAVE TEMP L18 MOH516HCAINV/A
L19           869 SEA ABB=ON  PLU=ON  L14 (L) L9
L20           143 SEA ABB=ON  PLU=ON  L14 (L) L10
L21           630 SEA ABB=ON  PLU=ON  L14 (L) L15
L22            42 SEA ABB=ON  PLU=ON  (L19 OR L20) AND L21
L23            12 SEA ABB=ON  PLU=ON  L19 AND L20
L24            52 SEA ABB=ON  PLU=ON  (L22 OR L23)
L25          2269 SEA ABB=ON  PLU=ON  L8 (10A) L9
L26          1145 SEA ABB=ON  PLU=ON  L8 (10A) L10
L27          2209 SEA ABB=ON  PLU=ON  L8 (10A) L15
L28           164 SEA ABB=ON  PLU=ON  L26 AND L27
L29           131 SEA ABB=ON  PLU=ON  L25 AND L27
L30            22 SEA ABB=ON  PLU=ON  L28 AND L29
L31            70 SEA ABB=ON  PLU=ON  L24 OR L30
L32            20 SEA ABB=ON  PLU=ON  L31 AND (L12 OR L13)
L33            65 SEA ABB=ON  PLU=ON  (L31 OR L32) AND L7
L34            65 SEA ABB=ON  PLU=ON  L33 AND ((HEMOGLOB?/OBI OR HAEMOGLOB?/OBI
                  OR HB/OBI) OR (OXYHEM? OR OXYHAEM?)/OBI)
L35            21 SEA ABB=ON  PLU=ON  L33 AND (?TETRAMER?/OBI OR (TETRA/OBI(W)MER
                  ?/OBI) OR 4MER/OBI OR (4/OBI(W)MER/OBI))
L36            38 SEA ABB=ON  PLU=ON  L33 AND (?POLYMER?/OBI OR POLYMD/OBI OR
                  ?OLIGOMER?/OBI)
L37            39 SEA ABB=ON  PLU=ON  L33 AND (STABILI?/OBI OR STABL?/OBI)
L38            54 SEA ABB=ON  PLU=ON  (L35 OR L36 OR L37)
L39            64 SEA ABB=ON  PLU=ON  L33 AND L14
L40            53 SEA ABB=ON  PLU=ON  L38 AND L39
L41            21 SEA ABB=ON  PLU=ON  L40 AND (L12 OR THERM? OR L13)

     FILE 'STNGUIDE' ENTERED AT 09:14:00 ON 12 MAY 2006
                D QUE

     FILE 'HCAPLUS' ENTERED AT 09:14:25 ON 12 MAY 2006
L42            43 SEA ABB=ON  PLU=ON  L33 AND L21
L43            15 SEA ABB=ON  PLU=ON  L41 AND L42
L44            43 SEA ABB=ON  PLU=ON  (L42 OR L43)
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                SAVE TEMP L44 MOH516HCA1B/A
                D QUE
L45          41 SEA ABB=ON  PLU=ON  L44 NOT L18

     FILE 'STNGUIDE' ENTERED AT 09:16:47 ON 12 MAY 2006

     FILE 'WPIX' ENTERED AT 09:17:12 ON 12 MAY 2006
L46          10 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L*** DEL      0 S L46 AND L14
L47           5 SEA ABB=ON  PLU=ON  L46 AND (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX
                OR HB/BIX)
                D TRI 1-5
                SAVE TEMP L47 MOH516WPIINV/A
L48         281 SEA ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX OR
                HB/BIX) (10A) (STABILI?/BIX OR STABL?/BIX)
L49         295 SEA ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX OR
                HB/BIX) (10A) (?POLYMER?/BIX OR POLYMD/BIX OR ?OLIGOMER?/BIX)
L50          46 SEA ABB=ON  PLU=ON  (HEMOGLOB?/BIX OR HAEMOGLOB?/BIX OR
                HB/BIX) (10A) (?TETRAMER?/BIX OR (TETRA/BIX(W)MER?/BIX) OR
                4MER/BIX OR (4/BIX(W)MER/BIX))
L51          11 SEA ABB=ON  PLU=ON  L48 AND L50
L52          32 SEA ABB=ON  PLU=ON  L48 AND L49
L53          20 SEA ABB=ON  PLU=ON  L49 AND L50
L54          51 SEA ABB=ON  PLU=ON  (L51 OR L52 OR L53)
L55          51 SEA ABB=ON  PLU=ON  L54 AND (AY<2004 OR PY<2004 OR PRY<2004)
L56          37 SEA ABB=ON  PLU=ON  L55 AND L48
L57          25 SEA ABB=ON  PLU=ON  L55 AND L50
L58          11 SEA ABB=ON  PLU=ON  L56 AND L57
                D TRI 1-11
L59           7 SEA ABB=ON  PLU=ON  L58 AND ((HEAT/BIX OR HEATING/BIX OR
                HEATED/BIX OR HEATS/BIX OR PREHEAT?/BIX OR (PRE/BIX(W)HEAT?/BIX
                ) OR TEMP/BIX OR TEMPERATURE/BIX) OR (AGE/BIX OR AGING/BIX OR
                AGEING/BIX OR AGES/BIX OR AGED/BIX OR TIME/BIX) OR THERM?/BIX)
L60          11 SEA ABB=ON  PLU=ON  L58 OR L59
                SAVE TEMP L60 MOH516WPI1B/A
L61           9 SEA ABB=ON  PLU=ON  L60 NOT L47
                D TRI 1-9

     FILE 'STNGUIDE' ENTERED AT 09:46:17 ON 12 MAY 2006
                D SAVED

     FILE 'HCAPLUS' ENTERED AT 09:47:14 ON 12 MAY 2006
                SAVE TEMP L1 MOH516HCAAPP/A

     FILE 'STNGUIDE' ENTERED AT 09:47:24 ON 12 MAY 2006
                D SAVED

     FILE 'MEDLINE' ENTERED AT 09:50:15 ON 12 MAY 2006

     FILE 'STNGUIDE' ENTERED AT 09:50:29 ON 12 MAY 2006

     FILE 'MEDLINE' ENTERED AT 09:53:51 ON 12 MAY 2006
L62          65 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L63          17 SEA ABB=ON  PLU=ON  L62 AND L8
L64           0 SEA ABB=ON  PLU=ON  L63 AND L10
L65           2 SEA ABB=ON  PLU=ON  L63 AND (L15 OR PRESERV?)
                D TRI 1-2
L66           5 SEA ABB=ON  PLU=ON  L63 AND L9
L67           5 SEA ABB=ON  PLU=ON  (L64 OR L65 OR L66)
                D TRI 1-5
```

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                SAVE TEMP L67 MOH516MEDINV/A
L68             QUE ABB=ON  PLU=ON  HEMOGLOBINS+PFT,OLD,NT/CT
L69        1358 SEA ABB=ON  PLU=ON  L8(15A)L15
L70         692 SEA ABB=ON  PLU=ON  L8 (10A) L10
L71        1173 SEA ABB=ON  PLU=ON  L8 (10A) L9
L72        2250 SEA ABB=ON  PLU=ON  L68 AND (L69 OR L70 OR L71)
L73         923 SEA ABB=ON  PLU=ON  L72 AND L69
L74         148 SEA ABB=ON  PLU=ON  L73 AND (L70 OR L71)
L75         107 SEA ABB=ON  PLU=ON  L74 AND L10
L76         101 SEA ABB=ON  PLU=ON  L75 AND L7
L77        1320 SEA ABB=ON  PLU=ON  L8 (15A) (L12 OR THERM?)
L78        6399 SEA ABB=ON  PLU=ON  L8 (15A)L13
L79          25 SEA ABB=ON  PLU=ON  L76 AND (L77 OR L78)
                D TRI 1-5
L80           3 SEA ABB=ON  PLU=ON  L79 AND L11
L81           0 SEA ABB=ON  PLU=ON  L80 AND (PRESERV? OR STORE OR STORAGE)
                D TRI L67 1-5
L82          12 SEA ABB=ON  PLU=ON  L79 AND L9 AND L10
L83          25 SEA ABB=ON  PLU=ON  L79 AND L15
L84          12 SEA ABB=ON  PLU=ON  L82 AND L83
                D TRI 1-12
L85          25 SEA ABB=ON  PLU=ON  L79 AND L8
L86          24 SEA ABB=ON  PLU=ON  L85/MAJ
                SAVE TEMP L84 MOH516MED1B/A

     FILE 'STNGUIDE' ENTERED AT 10:03:58 ON 12 MAY 2006

     FILE 'EMBASE' ENTERED AT 10:04:01 ON 12 MAY 2006
L87          47 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L88          12 SEA ABB=ON  PLU=ON  L87 AND L8
L89           5 SEA ABB=ON  PLU=ON  L88 AND (L9 OR L10 OR L15)
                SAVE TEMP L89 MOH516EMBINV/A
                D TRI 1-5

     FILE 'STNGUIDE' ENTERED AT 10:04:43 ON 12 MAY 2006

     FILE 'EMBASE' ENTERED AT 10:05:41 ON 12 MAY 2006
L90             QUE ABB=ON  PLU=ON  HEMOGLOBIN+PFT,OLD,NT/CT
L91             QUE ABB=ON  PLU=ON  "POLYMERIZED HEMOGLOBIN"+PFT,OLD,NT/CT
L92             QUE ABB=ON  PLU=ON  "HEMOGLOBIN DERIVATIVES"+PFT,OLD,NT/CT
L93        1327 SEA ABB=ON  PLU=ON  L8(15A)L15
L94         713 SEA ABB=ON  PLU=ON  L8(15A)L10
L95        1311 SEA ABB=ON  PLU=ON  L8(15A)L9
L96          20 SEA ABB=ON  PLU=ON  L93 AND L94 AND L95
L97        2318 SEA ABB=ON  PLU=ON  (L90 OR L91 OR L92) AND (L93 OR L94 OR
                L95)
L98             QUE ABB=ON  PLU=ON  "HEMOGLOBIN DERIVATIVE"+PFT,OLD,NT/CT
L99        2318 SEA ABB=ON  PLU=ON  ((L90 OR L91 OR L92) OR L98) AND (L93 OR
                L94 OR L95)
L100        933 SEA ABB=ON  PLU=ON  L99 AND L93
L101        105 SEA ABB=ON  PLU=ON  L100 AND L94
L102         20 SEA ABB=ON  PLU=ON  L101 AND L95
L103         20 SEA ABB=ON  PLU=ON  L96 OR L102
L104         14 SEA ABB=ON  PLU=ON  L103 AND (L11 OR L12 OR L13 OR THERM? OR
                PRESERV? OR STORE OR STORAGE OR STORING OR STORED)
L105         20 SEA ABB=ON  PLU=ON  L103 OR L104
L106         16 SEA ABB=ON  PLU=ON  L105 AND L7
                D TRI 1-4
L107         16 SEA ABB=ON  PLU=ON  L106 AND L15
L108         16 SEA ABB=ON  PLU=ON  L106 OR L107
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                SAVE TEMP L108 MOH516EMB1B/A

     FILE 'STNGUIDE' ENTERED AT 10:11:21 ON 12 MAY 2006
                D SAVED

     FILE 'BIOSIS, PASCAL, JICST-EPLUS, BIOENG, LIFESCI, CABA, BIOTECHNO,
     BIOTECHDS, VETU, VETB, DRUGU, DRUGB, SCISEARCH, CONF, CONFSCI, DISSABS'
     ENTERED AT 10:12:38 ON 12 MAY 2006
L109          259 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5)
L110           35 SEA ABB=ON  PLU=ON  L109 AND L8
L111            1 SEA ABB=ON  PLU=ON  L110 AND L15
L112            2 SEA ABB=ON  PLU=ON  L110 AND L10
L113            3 SEA ABB=ON  PLU=ON  L111 OR L112
                  D SCAN
                  SAVE TEMP L113 MOH516MULINV/A
                  D QUE L10
L114         2198 SEA ABB=ON  PLU=ON  L8(10A) L10
L115         5045 SEA ABB=ON  PLU=ON  L8(15A) L15
L116          349 SEA ABB=ON  PLU=ON  L114 AND L115
L117         4628 SEA ABB=ON  PLU=ON  L8 (10A) L9
L118           61 SEA ABB=ON  PLU=ON  L116 AND L117
                  D QUE L7
L119           51 SEA ABB=ON  PLU=ON  L118 AND L7
                  D QUE L108
L120           38 SEA ABB=ON  PLU=ON  L119 AND (L11 OR L12 OR L13 OR THERM? OR
                  PRESERV? OR STORE OR STORAGE OR STORING OR STORED)
L121           51 SEA ABB=ON  PLU=ON  L119 OR L120
                  SAVE TEMP L121 MOH516MUL1B/A
                  D SAVED

     FILE 'STNGUIDE' ENTERED AT 10:29:38 ON 12 MAY 2006
                D QUE STAT L44
                D QUE STAT L60
                D QUE STAT L84
                D QUE STAT L108
                D QUE STAT L121

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI,
     BIOTECHNO, DRUGU, SCISEARCH, DISSABS' ENTERED AT 10:31:15 ON 12 MAY 2006
L122           77 DUP REM L44 L60 L84 L108 L121 (56 DUPLICATES REMOVED)
                       ANSWERS '1-43' FROM FILE HCAPLUS
                       ANSWERS '44-51' FROM FILE WPIX
                       ANSWERS '52-61' FROM FILE MEDLINE
                       ANSWERS '62-65' FROM FILE EMBASE
                       ANSWERS '66-67' FROM FILE BIOSIS
                       ANSWER '68' FROM FILE PASCAL
                       ANSWERS '69-70' FROM FILE BIOENG
                       ANSWER '71' FROM FILE LIFESCI
                       ANSWERS '72-73' FROM FILE BIOTECHNO
                       ANSWERS '74-75' FROM FILE DRUGU
                       ANSWERS '76-77' FROM FILE DISSABS

     FILE 'STNGUIDE' ENTERED AT 10:31:51 ON 12 MAY 2006

     FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI,
     BIOTECHNO, DRUGU, DISSABS' ENTERED AT 10:32:03 ON 12 MAY 2006
                D IBIB ED AB HITIND

     FILE 'STNGUIDE' ENTERED AT 10:32:06 ON 12 MAY 2006
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FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' ENTERED AT 10:32:15 ON 12 MAY 2006
D IBIB ED AB HITIND 2-43

FILE 'STNGUIDE' ENTERED AT 10:32:21 ON 12 MAY 2006

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' ENTERED AT 10:33:13 ON 12 MAY 2006
D IALL ABEQ TECH ABEX 44-51

FILE 'STNGUIDE' ENTERED AT 10:33:17 ON 12 MAY 2006

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, BIOENG, LIFESCI, BIOTECHNO, DRUGU, DISSABS' ENTERED AT 10:34:03 ON 12 MAY 2006
D IBIB ED AB HITIND 52-77

FILE 'STNGUIDE' ENTERED AT 10:34:08 ON 12 MAY 2006
D QUE STAT L18
D QUE STAT L47
D QUE STAT L67
D QUE STAT L89
D QUE STAT L113

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS' ENTERED AT 10:36:05 ON 12 MAY 2006
L123 15 DUP REM L18 L47 L67 L89 L113 (12 DUPLICATES REMOVED)
ANSWERS '1-9' FROM FILE HCAPLUS
ANSWER '10' FROM FILE WPIX
ANSWERS '11-12' FROM FILE MEDLINE
ANSWER '13' FROM FILE EMBASE
ANSWERS '14-15' FROM FILE BIOSIS

FILE 'STNGUIDE' ENTERED AT 10:36:10 ON 12 MAY 2006

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS' ENTERED AT 10:36:20 ON 12 MAY 2006
D IBIB ED AB 1-15

FILE 'STNGUIDE' ENTERED AT 10:36:23 ON 12 MAY 2006

FILE 'STNGUIDE' ENTERED AT 10:36:51 ON 12 MAY 2006

FILE HOME

FILE ZCAPLUS

FILE COVERS 1907 - 12 May 2006 VOL 144 ISS 21
FILE LAST UPDATED: 11 May 2006 (20060511/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE HCAPLUS

FILE COVERS 1907 - 12 May 2006 VOL 144 ISS 21
FILE LAST UPDATED: 11 May 2006 (20060511/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 5, 2006 (20060505/UP).

FILE WPIX
FILE LAST UPDATED: 10 MAY 2006 <20060510/UP>
MOST RECENT DERWENT UPDATE: 200630 <200630/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

FILE LWPI
LWPI IS A STATIC LEARNING FILE
>>> PATENT DRAWINGS AVAILABLE FOR DISPLAY <<<

FILE MEDLINE
FILE LAST UPDATED: 11 MAY 2006 (20060511/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 11 May 2006 (20060511/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 10 May 2006 (20060510/ED)

FILE PASCAL
FILE LAST UPDATED: 8 MAY 2006 <20060508/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 1 MAY 2006 (20060501/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE BIOENG
FILE LAST UPDATED: 12 MAY 2006 <20060512/UP>
FILE COVERS 1982 TO DATE

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN THE BASIC INDEX <<<

FILE LIFESCI
FILE COVERS 1978 TO 14 Apr 2006 (20060414/ED)

FILE CABA
FILE COVERS 1973 TO 3 May 2006 (20060503/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.

>>> BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004 <<<

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN /CT AND BASIC INDEX <<<

FILE BIOTECHDS
FILE LAST UPDATED: 10 MAY 2006 <20060510/UP>
FILE COVERS 1982 TO DATE

>>> USE OF THIS FILE IS LIMITED TO BIOTECH SUBSCRIBERS <<<

FILE VETU
FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>
FILE COVERS 1983-2001

FILE VETB
FILE LAST UPDATED: 25 SEP 94 <940925/UP>
FILE COVERS 1968-1982

FILE DRUGU
FILE LAST UPDATED: 12 MAY 2006 <20060512/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE DRUGB
>>> FILE COVERS 1964 TO 1982 - CLOSED FILE <<<

FILE SCISEARCH

FILE COVERS 1974 TO 11 May 2006 (20060511/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONF
FILE LAST UPDATED: 23 DEC 2005 <20051223/UP>
FILE COVERS 1976 TO 2005.

<<< CONF IS NO LONGER BEING UPDATED AS OF JANUARY 2006 >>>

FILE CONFSCI
FILE COVERS 1973 TO 10 Apr 2006 (20060410/ED)

CSA has resumed updates, see NEWS FILE

FILE DISSABS
FILE COVERS 1861 TO 28 APR 2006 (20060428/ED)

PARTICULAR PURPOSE, AND SHALL NOT BE LIABLE FOR DAMAGES OF ANY KIND OR LOST PROFITS OR OTHER CLAIMS RELATED TO THE LICENSED MATERIALS OR THEIR USE.

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